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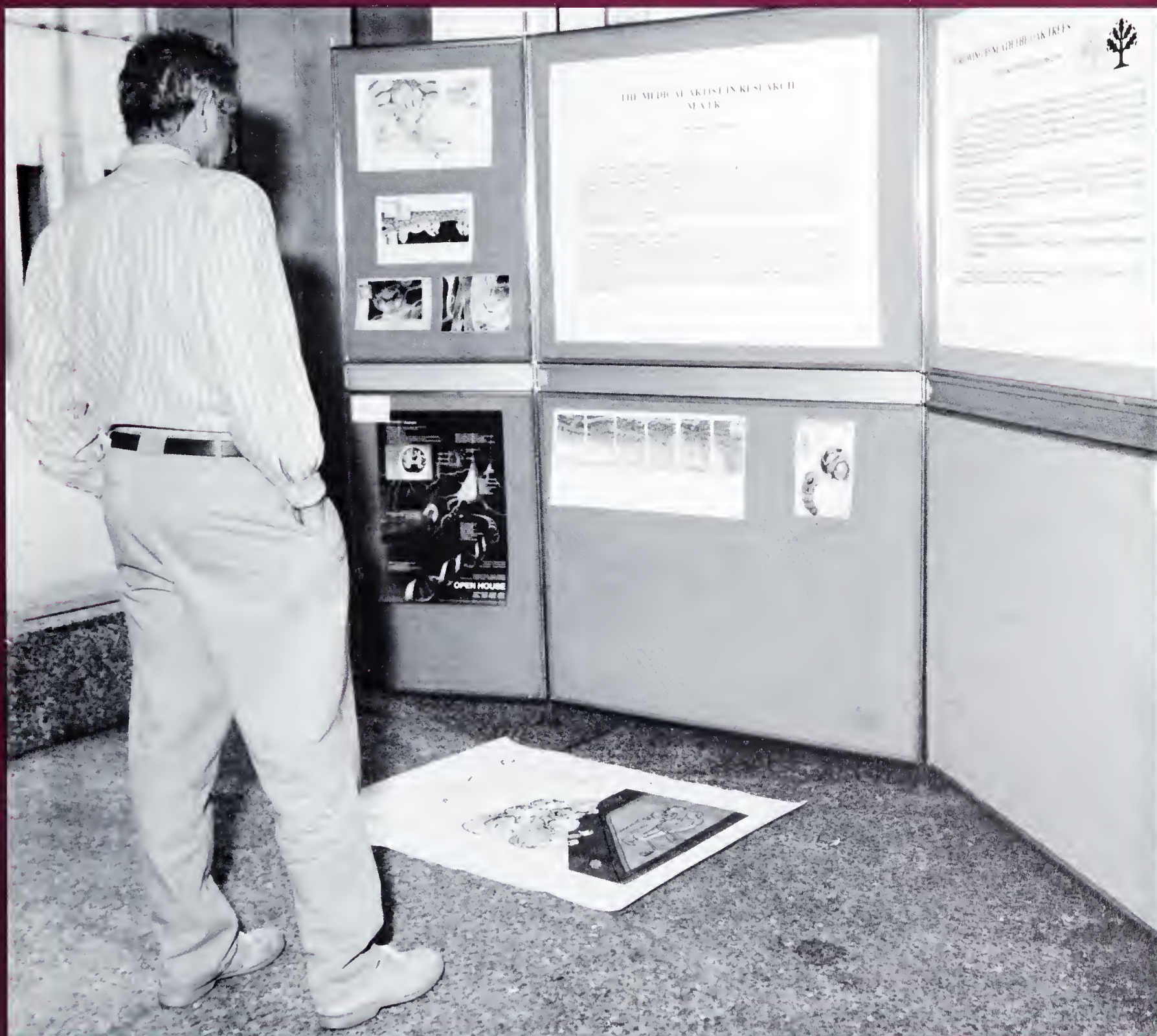
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University of Toronto **MEDICAL JOURNAL**

Vol. LXVI

Supplement 1

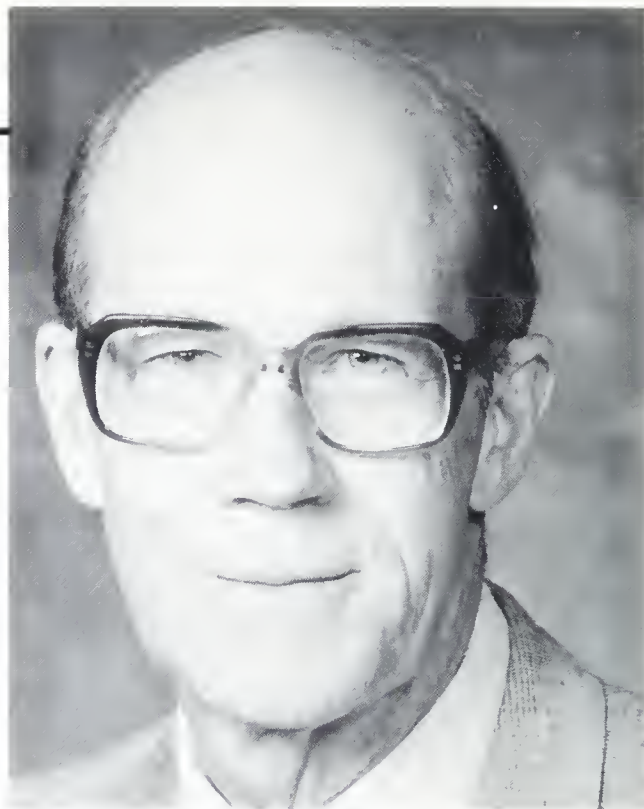
Undergraduate Medical Research



at the University of Toronto



Dean Dirks
Dean, Faculty of Medicine



Dr. R. Fleming
Associate Dean, Undergraduate Curriculum

Undergraduate Medical Student Research Day

The Medical Research Day is a highly significant moment in the events of a Faculty of Medicine. This Faculty has the strongest commitment to research and scholarship. The day brings together, for examination and discussion, the superb research work that students have done in a whole variety of fields during their summer fellowships.

I again enjoyed viewing the spectrum of research that was demonstrated. I felt a great sense of pride in realizing that our own undergraduate medical students were performing so well in their research milieu. I could readily foresee that they will join many illustrious members of this Faculty and this University who have had such distinguished research careers. I visualize that among you, many in the future will make similar distinguished contributions to research and change our current medical knowledge. It is so important to understand how knowledge is developed and where advances in clinical medicine come from.

The Faculty of Medicine of the University of Toronto is Canada's leading research faculty and is one of the leading ones in North America. I hope that you will take much satisfaction and fulfillment in your own research and will treasure the experience and lessons derived from it.

You are entering the practice of medicine at an exciting time when virtually every day there are new scientific developments in the fields of biology and medicine. An academic career in medicine is a very worthy goal. I hope that you will be dearly tempted to take it up.

With best wishes for a successful day. Congratulations on your presentations.

John H. Dirks
Dean
Faculty of Medicine

Summer Scholarship Program

The Faculty of Medicine is fortunate to offer a number of scholarships to first and second year medical students who undertake research projects during the summer.

This year 90 such scholarships are available, each in the amount of approximately \$3000. Scholarships have been provided by a number of private donors and agencies. Amongst these, the Faculty Scholarship Trust Fund provides 25 scholarships, our Medical Alumni Association provides 15, and the Medical Research Council of Canada provides 38. Other scholarships are provided by the Heart and Stroke Foundation of Ontario (3), CIBA Geigy (1), Leukemia Research Foundation (1), Lela Parlow Cancer Research Fellowship (1), R.J. Wilson Award (1), Nu Sigma Nu Fraternity (2), Women's Breast Cancer Foundation (2), and the Pharmaceutical Manufacturers Association of Canada (3). Some scholarships are designated for specific areas of research, and others are more general.

All Year 1 and Year 2 students who are enrolled in our undergraduate medical program are eligible to apply for a summer scholarship. Over 400 opportunities that qualify for summer scholarships are listed in the Summer Scholarship Catalogue, and amongst these are many outstanding research experiences. Included in the catalogue is a list of Faculty members willing to act as supervisors. Students may also apply for scholarships to fund opportunities not listed in the catalogue.

Applications providing a detailed description of the proposed project and approved by the supervisor must be received in the Undergraduate Medical Education Office by mid-February. All applications are reviewed on the basis of the specific details of the proposal received, the commitment of the student and the supervisor to the project, and the relevance to the student's education and career goals. Scholarships are awarded on a competitive basis.

The program, together with the elective time available during the academic year, provides an excellent opportunity for students to develop or continue their research interests as well as to explore future career interests in basic or clinical research.

Ross Fleming
Associate Dean
Undergraduate Curriculum

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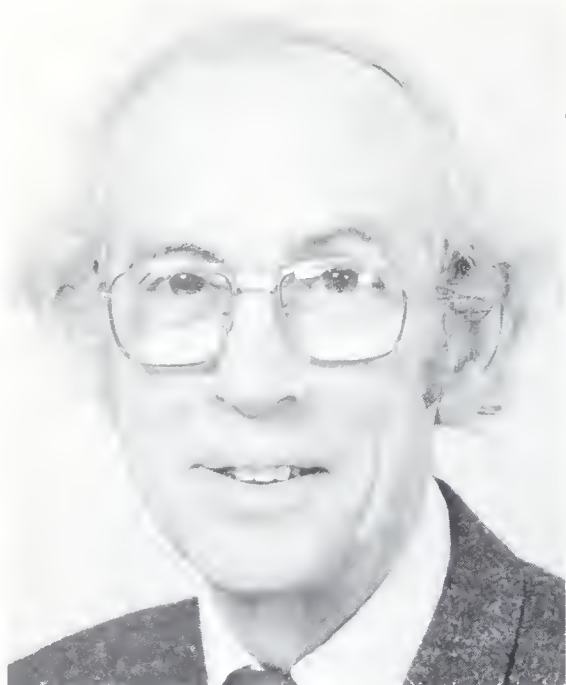
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Student Research Day, 1988

The third annual student research day was held on December 6, 1988. Sixty-two students presented posters. The overall caliber of poster presentations was viewed as excellent. On the other hand, the Symposium on "The Heart", involving a very brief statement from individual students followed by general comments, was not quite as successful, primarily because of the brevity of presentations. This year, 1989, I think we should drop the symposium and concentrate on posters only.

Three students, Shelley Boyd (Year 1), Bach Vu (Year 3) and Gil Mildroni (Year 3), were invited to present their posters at the National Student Research Forum in Galveston in April of 1989. Funding for this trip was provided by the Alumni Association and I express my gratitude to Dr. Ruth Kurdyak for persuading the Alumni Association to provide funds. Poster presentations at the "National" in Galveston are a minor part of the event, which focuses on verbal presentations. In order to compete successfully at Galveston, having selected 3 representatives from our medical school, I suggest in the future that we provide opportunities for improvement of their verbal presentations.

Following the poster session, a successful dinner was held for participants and their research supervisors. Dean Dirks pointed out that the involvement in research in undergraduate medical school was the best predictor of career research involvement. Dr. Tom Salerno, the keynote speaker, described the life of a clinical scientist as an exciting, busy and fulfilling one.

Student Research Day has been singularly successful in achieving its goal of providing students with a public opportunity to display their research work. However, it could do more. Participation of 62 students out of a total of 1000 undergraduates means that only 1 in 16 engages in the event. Moreover, we have no evidence to indicate that Research Day influences students to participate in research.

There are many ways for students to take on research projects, including the MD/PhD and

the UPMS programmes and summer scholarships. There is no research requirement as an obligatory part of the undergraduate curriculum. Nor do we have in place a system that actively promotes and encourages students to engage in research projects. The question is: should we, both faculty and students, be doing more to promote student research? One way to get started in this direction is to put Student Research on the Agenda for Orientation Day, by holding a Student Research Forum organized and run by previous participants of Research Day, by enrollees in the MD/PhD and UPMS programmes, and by Summer Scholarship grantees, together with a cross section of faculty scientists. The focus of this proposed forum might be, "How do I get involved in research?", with emphasis on "how". To this end I will speak with the Assistant Dean of Student Affairs to see if we can get the forum off the ground for our 1989 Orientation Day.

Niall Byrne, Ph.D.

Student Research Day Organizer

EDITORIAL

The work presented in this special issue of the University of Toronto Medical Journal represents the fruition of thousands of hours of work by dozens of medical students united by a common vision: the desire to learn more about the nature of man. I think most would agree that they have learned a good deal about themselves along this journey.

This Supplementary Issue of the Journal was assembled to celebrate the research achievements of undergraduate medical students at U. of T. It is published in conjunction with the third annual Undergraduate Medical Student Research Day, a new tradition in the Faculty of Medicine which has become more successful each year.

This is the second year that the Journal has published the abstracts presented at the Research Day. This year, we wished to expand the contribution of the Faculty members to this issue and to highlight undergraduate research in the broader sense. Thus, we are delighted by the response shown by Deans Dirks and Fleming, and by Drs. Murray, Bayliss, and Whiteside. Mitesh Mehta and Tiui Kask of IMS deserve much of the credit for the production of this issue. And a very special thanks must go to Dr. Niall Byrne, who once again put in a superb effort in organizing the Research Day as well as contributing his insights to this issue. Undergraduate Medical Student Research Day allows students to present their work as posters and 10-minute talks, the formats used in national and international scientific meetings. It is a valuable experience even for those students who will not continue on in research careers. We feel that the effort put in by the students deserves wider recognition, and we are proud to present this special issue as the means to this end.

Ian R. A. Park, Ph.D., 9T0
Supplement Editor

Annual Student Research Day – A Look to the Future

This year I had the honour and pleasure of evaluating the poster presentations at the Third Annual Student Research Day. As I interviewed the participants, the new dimension that investigation was adding to their career development became remarkably evident. Reflection on my undergraduate days at the University of Toronto Medical School brings to mind how my perspective about medical research has changed.

As a medical student, my main desire was to become a full-time clinical practitioner. Eager to apply my hard-won knowledge and clinical skills, I could hardly wait to enter clinical clerkship. Every summer, even before medical school, I worked in hospitals and enjoyed interacting with patients and their families. At that time, bedside medicine was all important. Although I was aware that many Faculty members were engaged in medical research on the upper floors of the Medical Sciences Building and in the teaching hospitals, this activity seemed quite secondary to the prime directive of medicine – diagnosis and treatment of the sick. When I occasionally read *The New England Journal of Medicine* in those days, the clinical pathological conferences captured my interest, not the scientific articles.

Throughout my residency, particularly in subspecialty (Nephrology) training, I became more and more aware of limitations in clinical knowledge. My patients suffered from diseases that could be neither prevented nor treated short of dialysis and renal transplantation. In my final year of postgraduate training, I entered the world of laboratory-based research. Not only was my intellectual curiosity reawakened (it disappeared in Medical School) but, more importantly, I began to realize that scientific investigation and clinical practice are partners. Problem-solving and the application of the scientific method are critical to both. Knowledgeable expertise and creativity are required to generate hypotheses and conduct investigation at the bedside as well as in the laboratory. The clinician-scientist and practising physician are equally committed to eradicating disease.

I regret this realization didn't occur earlier in my training because, ultimately, I chose the path of the career investigator. Now, it is the scientific articles in the *New England Journal of Medicine* that attract my attention. Research Day is one of the ways this message is now communicated to and, more significantly, by our medical students.

The basic science and clinical investigators within our Faculty provide many superb opportunities to those undergraduates who wish to pursue research during the summer months and elective time. At Research Day, the spectrum of topics reflected the widely-varying interests of the students and supervisors. These



must nurture, as early as possible, the career development of those who will become expert medical educators and creative investigators. Student Research Day now provides a forum in which scientific investigation is given a place of prominence in the undergraduate curriculum. The supportive attitude which prevails on this day must continue and expand throughout the year.

Catherine I. Whiteside
M.D., Ph.D., F.R.C.P. (C)

ranged from mathematical modelling of transepithelial transport, the identification of novel recombinant DNA probes, new diagnostic tests of specific brain dysfunction to psychosocial factors governing public health in rural Ethiopia. Common to all of these presentations were the enthusiasm of the participants and the quality of their displays. A number of students indicated with pride that they had or would be presenting their research at scientific conferences, a mark of successful peer review.

All the students who participated, despite busy academic schedules, spent many hours preparing their creative and very successful posters. This time allotment represents only a fraction of the time that many now spend in writing manuscripts for publication. These students have learned that investigating the mechanisms of disease is as important as treating the patient. A number of the students who participated in Research Day will undoubtedly continue to pursue a career in medical research, accepting the challenge of scientific discovery. Those who become full-time clinicians will have a better understanding of how medical research helps to advance the delivery of health care.

The role of the Faculty should not be overlooked. Just as bedside teaching demands a major commitment from the physician, so does the supervision of medical student research. As I interviewed the students, many spontaneously praised their supervisors, who are impressive role models.

Student Research Day is now a successful annual event, thanks to the dedication and vision of Faculty members such as Niall Byrne. As a member of the Centre for Studies in Medical Education, he wholeheartedly supports undergraduate research activity as an important learning experience.

In four short years, medical students personally encounter only a small number of clinical teachers. Most are clinician-teachers, some are clinical investigators, and a very few are basic scientists. How can we inform medical students about the significance of medical research? I believe the answer is to create a teaching environment in which medical students, interns, and residents experience investigation and clinical practice as a true partnership. It is not good enough to train superb clinicians. We



Research Day

What do I think of when I think of Research Day? That's the question I was posed by Ian Park and Ted Davies. Here's a kind of stream of conscious response.

Firstly, I think of Michael Pare (Meds 8T8) and Niall Byrne, who started it all. Michael had experienced the Research Day at McGill and suggested its introduction here. Niall did a lot of the groundwork to make the first one possible, and has continued to be the key organizer, putting in a lot of extra hours making sure things go smoothly and that the dinners in Hart House or Massey College are always memorable.

Then I think of all the talented participants, 50-60 per year. My mind runs over the excellent oral presentations that I've heard, covering almost every aspect of basic and clinical science and community health. Then the posters, most of very high quality. And the questions and answers on their content.

Yes, that's what research is all about. Asking questions and attempting to get answers. Often not finding answers to the questions posed, but coming up with an answer to a different question, not considered when the project was initially discussed. Finding out that knowledge is not as neatly organized as the formal lectures in medical school suggest. Indeed, discovering that practically nothing is known about so

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Cardiovascular Research Symposium

The enthusiastic participation of students and staff in this year's Research Day bodes well for the future of medical research in the Faculty of Medicine. This issue of the University of Toronto Medical Journal confirms the wide-ranging interests of our students and their determination to pursue environments where their research hypotheses can be tested. The quality of the work was outstanding and would be competitive at national and international levels.

Fifteen excellent posters were presented by students working in the cardiovascular sciences. These represented diverse areas of interest with five participants from each of the first three years of Medicine. This concentration of effort spurred the organizers to convene a Cardiovascular Research Symposium. We asked each student to speak briefly on why they thought their area of research was important and where they thought it was going in the future.

In a clinical test of procainamide, Lisa Kellet found that its intravenous effectiveness in the electrophysiologic laboratory did not predict its clinical usefulness in suppressing ventricular tachycardia in the long term. In another study, Joel Kirsh found that both nodal and accessory conduction pathways consistently scaled the ventricular responses to atrial fibrillation, with implications for pharmacological intervention in this arrhythmia.

Endothelial injury is an atherogenic stimulus. Paul Mazzoli found that the tendency for endothelial repair by cell spreading depends on reduced interaction with the substratum. Future work will relate these cell culture findings to the *in vivo* scenario.

In a study of frog sarcoplasmic reticulum, Anne McLeod found calsequestrin where conventional wisdom suggested it might not exist. Further studies will unify concepts of excitation-contraction coupling if calsequestrin is localized in junctional sarcoplasmic reticulum.

Anne Shin discovered that the combina-

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POSTERS PRESENTED

PART A – BASIC RESEARCH

DOPAMINE (D) INFUSION CAUSES RENAL SYMPATHETIC DENERVATION IN RATS IN HEMORRHAGIC SHOCK

Mahmood Abedi*, A.D. Baines and T. Dalle Ave
Department of Clinical Biochemistry, University of Toronto,
Toronto, Ontario

Patients in shock are frequently infused with D for its cardiotonic and renal vasodilatory properties. Free radicals produced by patients in shock have been observed to convert some D to the neurotoxin 6-hydroxydopamine (6OHD). The present study was designed to measure the extent of renal denervation produced by D infusion in rats in hemorrhagic shock.

Anaesthetized male Wistar rats (250-300g) were infused with D (15µg/kg/min) for 90 minutes before and 90 minutes following removal of 4-5 ml of blood. They were then allowed to recover for 3-7 days before their kidneys were removed. Tissue catecholamines were measured using HPLC with coulometric detection. Renal cortical norepinephrine (NE) content was used to quantify sympathetic innervation. We found that the rats which received D and were hemorrhaged had significantly lower renal cortical NE than control rats (0.18 ± 0.06 vs 0.62 ± 0.03 nmol/g; $p = 0.0008$ ANOVA). Hemorrhage alone or D infusion alone also decreased NE level (0.27 ± 0.02 and 0.33 ± 0.06). The extent of NE reduction was similar to that produced by 10mg/kg 6OHD IV (0.26 ± 0.19). Hypoxanthine and xanthine oxidase, which were infused to produce free radicals, did not reduce NE. We conclude that 6OHD produced during D infusion of hypovolemic rats may destroy peripheral sympathetic nerve terminals.

CLONING AND EXPRESSION OF MYELIN-ASSOCIATED GLYCOPROTEIN

P. Johnson, M.B. Tropak, M. Arquint*, W. Abramow-Newerley, R. Sadoul, M. Schachner, R. Dunn and J. Roder
Departments of Medical Genetics and Immunology, University of Toronto; University of Heidelberg, Heidelberg, West Germany

Myelin-associated glycoprotein (MAG) is a putative cell adhesion molecule (CAM) involved in glial-neural cell interactions which result in myelination. In order to study and confirm its function in myelination, we have cloned and sequenced the cDNA coding for MAG. From its sequence we determined that MAG is a member of the immunoglobulin supergene family and that it is related to the well-characterized neural cell adhesion molecule N-CAM. Furthermore, we have established that MAG is phosphorylated both *in vitro* and *in vivo*, which confirms our predictions made on the basis of sequence characteristics in the protein's cytoplasmic domain. We have also shown that the two forms of MAG (67 kD and 72kD) are generated by alternative splicing of MAG transcripts. We have expressed the cDNAs for p67 and p72 MAG in 3T3 cells. Purified recombinant p67 and p72 MAG expressed in 3T3 cells, when incorporated into the membrane of liposomes, is able to bind to neurites in a manner similar to MAG isolated from brain. This suggests a cell-adhesive function for MAG and indicates that a receptor for MAG is present in neurites.

We are now in a position to look at the role of phosphorylation and alternative splicing in MAG function. A soluble form of MAG has been engineered which will be useful in elucidating its three-dimensional structure as well as in identifying and cloning the neuronal receptor for MAG.

COMPARISON OF ROE'S AND BRETSCHNEIDER'S CARDIOPLEGIC SOLUTIONS IN A CANINE MODEL OF CARDIOPULMONARY BYPASS

Robert A. Axford-Gatley*, Bradley G. Bush, Donald A.G. Mickle, Alex D. Romaschin and Gregory J. Wilson
Department of Cardiovascular Surgery, Toronto General Hospital, Toronto, Ontario

We have compared the quality of myocardial protection provided by Roe's and Bretschneider's cardioplegic solutions in a canine model of cardiopulmonary bypass with hypothermic (27°C), multidose administration of cardioplegia during 4.5 hours of ischemic arrest. The ischemic interval was followed by 60 minutes of reperfusion. Bretschneider's solution (Group I, 6 dogs) preserved myocardial ATP near preischemic levels and maintained coronary effluent pH near 7.0 throughout the ischemic interval, whereas Roe's solution (Group II, 6 dogs) allowed progressive acidosis and depletion of ATP ($P < 0.005$ versus preischemic). Group I had supranormal left ventricular function during reperfusion ($>100\%$ of preischemic function) but Group II regained only 40-75% of preischemic function ($P < 0.0001$). Group I had $2.82\% \pm 3.61\%$ (S.D.) necrosis of heart mass while Group II had $9.33\% \pm 8.26\%$ necrosis ($P < 0.01$). Roe's and Bretschneider's formulations differ most notably in buffering capacity, with the histidine-buffered Bretschneider solution having up to 60-fold greater buffering capacity than the tris(hydroxymethyl)aminomethane-buffered Roe solution, at 27°C in the physiological range of pH.

We conclude that the quality of myocardial protection provided by Bretschneider's solution was superior to Roe's solution. Although the formulations of these solutions differ in several respects, the effective buffering of Bretschneider's solution with histidine was most likely the basis of its superiority to Roe's.

EFFECT OF REFRACTORINESS ON THE ELECTRICAL CONTROL ACTIVITY OF GASTROINTESTINAL SMOOTH MUSCLE

David W. Bell* and Berg L. Bardakjian
The Institute of Biomedical Engineering, University of Toronto,
Toronto, Ontario

The myogenic control system in the mammalian gastrointestinal tract is manifested by periodic depolarizations of the smooth muscle cells which constitute autonomous electrical oscillations called the electrical control activity (ECA). The nature of the ECA in the stomach behaves electrically like a population of coupled nonlinear oscillators. A mapped clock oscillator model employing nonlinear dynamics has been employed to study the effect of refractoriness on the interaction between two bidirectionally coupled oscillators. Four coupling types have been employed: (1) Gamma, influencing oscillator entrainability; (2) Phi, influencing oscillator frequency; and for both (3) Direct, intrinsic clock variables are coupled; and (4) Indirect, oscillator outputs are coupled. Other parameters such as the order of the refractory function (N) are also studied.

Results show: (1) for gamma coupling the entrainment frequency (EF) of the two oscillators will be influenced the greatest by the oscillator with the least refractoriness and that the phase lag (PL) between the oscillators increases as refractoriness increases; (2) for phi coupling the EF of the two oscillators decreases as refractoriness increases and that the PL can increase (indirect phi) or decrease (direct phi) depending on the type of coupling employed; (3) the above trends are most consistent when N was higher rather than lower; and (4) for frequency entrainment to occur at all, a stronger degree of coupling is required for phi than for gamma coupling. Thus, refractory properties may have a significant role in governing gastric oscillator interaction.

STRUCTURE-FUNCTION RELATIONSHIPS OF THE VOLTAGE-GATED SODIUM CHANNEL

S.R. Boyd*, V.J. Auld, A.L. Goldin, J.M. Dunn, K. Johnston and R.J. Dunn

Department of Medical Genetics, University of Toronto, Toronto, Ontario

All living cells have electrochemical gradients across their plasma membrane yet only some are electrically excitable. Electrical excitability is mediated by voltage-gated ion channels. These integral membrane proteins detect a perturbation in their electrochemical environment, and perpetuate this change by allowing ions to move passively through their pore. We have cloned the cDNA encoding the α IIA subunit of a voltage-gated sodium channel from rat brain. Several structural models derived from analysis of the primary sequence have been proposed. At present, low levels of expression and the requirement for membrane insertion have precluded direct structural analysis (by X-ray crystallography for instance). We are therefore using indirect methods to test and modify present models. Expression of the α IIA cDNA in *Xenopus* oocytes demonstrates that an additional low molecular weight component is necessary for "wild-type" channel conductance. Further, reported channels implicate these in voltage-current relationships. At present, we are producing region-specific antisera against the sodium channel to assess its transmembrane topology. These antisera are being raised against recombinant proteins expressed in *E. coli*. Antisera directed against the region of the channel known to be phosphorylated *in vivo* will also be used to assay its functional significance.

IN VITRO PREDICTORS OF IN VIVO RADIORESPONSE IN MURINE TUMOURS

Robert Bristow* and Richard Hill

The Ontario Cancer Institute and the Department of Medical Biophysics, University of Toronto, Toronto, Ontario

Radiation therapy is a major form of cancer treatment and is usually given as a series of daily 2 Gy fractions. Historically, micro-environmental and cellular kinetic factors (rather than inherent genetic factors) were thought to determine the radiocurability of tumours. Recent emphasis on the low-dose region of human *in vitro* radiation survival curves (that part of the curve relevant to clinical radiation doses) has shown that there may be a correlation between *in vitro* radiosensitivity and clinical radiocurability. We tested this hypothesis using a spectrum of transplantable murine tumours representing differing histopathological types. For each tumour cell line, *in vitro* radiation survival and levels of intracellular glutathione (a possible radioprotector; levels measured using HPLC analysis) were determined to compare to the *in vivo* radioresponse following fractionated radiation treatment. The *in vivo* radioresponse (the same cell lines growing as solid tumours in animals) was measured using *in situ* growth delay and excisional and *in vivo* responses on a 1:1 basis for each tumour cell line studied. The present results show an excellent correlation between *in vitro* low-dose radiation survival and *in vivo* radioresponse. These initial studies support the concept that intrinsic genetic radiosensitivity is an important determinant of radioresponse and that *in vitro* radiation characteristics of tumour lines may predict clinical radiotherapeutic outcomes, allowing modification and individualization of therapy for patients.

PHOTOAFFINITY LABELLING OF HUMAN BRAIN D2 DOPAMINE RECEPTORS IN SCHIZOPHRENIA, ALZHEIMER'S, PARKINSON'S AND HUNTINGTON'S DISEASES

N.H. Bzowej*, H.B. Niznik and P. Seeman

Department of Pharmacology, University of Toronto, Ontario

Considerable evidence exists to suggest abnormal brain dopamine transmission in schizophrenia, Alzheimer's, Parkinson's and Huntington's diseases. The molecular structure of the striatal D2 receptor-binding subunit in these diseased brains was identified by photoaffinity labelling with [^{125} I]Azido-NAPS. In all diseased tissues studied, [^{125} I]Azido-NAPS specifically and covalently labelled a broad band of $M_r \approx 94,000$, as assessed by autoradiography following sodium dodecyl sulfate polyacrylamide gel electrophoresis, which was similar to human control brain D2 subunits and that observed in canine striatal membranes. Further work will assess the relative electrophoretic mobilities of deglycosylated photo-labelled D2 binding subunits in these tissues.

This work was supported by the MRC of Canada, The Canadian Friends of Schizophrenics, OMHF and NARSAD.

MICROBICIDAL ROLE OF INFLAMMATION IN GRAM NEGATIVE INFECTION

W. Chan* and H.Z. Movat

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With live *E. coli* 055:B5 the magnitude and kinetics of ^{51}Cr -PMN accumulation in rabbit skin was compared with levels of circulating PMNs, increase in vasopermeability (^{125}I -albumin) and the recovery of colony forming units (CFUs) in normal, neutropenic and immunized animals. PMN emigration and enhanced vasopermeability peaked in 2-4 h old lesions ($2 \times 10^7 - 10^9$ *E. coli*/site), but 24 h lesions had to be elicited to prevent subsequent development of a neutropenia (Am. J. Pathol. 125:1-9, 1986). In normal rabbits lesion homogenates indicated early (1-2 h) bacterial multiplication, followed by diminished CFUs. The latter correlated with the peak emigration of PMNs; TEM demonstrated phagocytosis of the bacteria by the PMNs. Animals that recovered from neutropenia (Mustargen) had only an early (1-4 h) increase of CFUs, followed by bacterial clearance, whereas those with persistent low PMN counts had a prolonged and marked increase of CFUs. Compared to normals, fewer PMNs accumulated and there was less plasma exudation in neutropenic rabbits, and there was a delayed inflammatory reaction during recovery from neutropenia. In neutropenic rabbits there was severe dermal necrosis. In actively immunized animals and with passive local transfer of anti-*E. coli* antiserum fewer PMNs accumulated, but these were able to cope with bacterial elimination like normal controls.

A VOLUME OVERLOAD MODEL OF CONGESTIVE HEART FAILURE

Grace Chua*, Michèle Brûlé, Bik Nanar, Jorge Cruz, Patty Boylen and David Salter

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This study was undertaken to develop a small-animal model of congestive heart failure (CHF) using volume overload in 2 species. An aorto-caval (A-C) fistula was created in 20 rabbits. Each animal was examined daily for one month and then sacrificed. Echocardiography was used to follow the development of CHF in 8 rabbits. Cardiac morphometric and histologic analysis was done in the study animals, 2 sham operated and 8 control animals. Seven A-C fistula rabbits died before one month because of either acute pulmonary edema (2) or hind limb paralysis (5). Twenty rats were also studied in a similar manner (15 aorto-caval fistulae, 4 sham and 1 control). Eight A-C fistula rats died before one month because of acute pulmonary edema (3), hind limb paralysis (3), hemorrhage (1) or severe CHF (1). Overall, only 4 rabbits (20%) clearly developed congestive heart failure as evidenced by a 40% increase in LV-body weight ratio compared to the normal, sham and failed fistula group ($p < 0.05$). None of the rats that survived 1 month had an open fistula. While chronic volume overload using aorto-caval fistulae is a widely-accepted model to examine CHF in large animals, in small animals the relatively increased ratio of arteriovenous shunt to ventricular size greatly narrows the margin of cardiac tolerance and reduces the reproducibility and reliability of this model to study chronic ventricular failure.

EFFECTS OF CHRONIC DIETARY GLUCOSE AND FRUCTOSE ON FATTY ACID UPTAKE BY THE PERFUSED RAT LIVER

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The purpose of this study was to examine the effects of chronic carbohydrate (glucose and fructose) feeding on the incorporation of exogenous and endogenous fatty acid into hepatic very low density lipoprotein triglyceride (VLDL-TG). A perfused rat liver model with tritiated oleic acid as exogenous fatty acid substrate was used. The data showed that glucose and fructose induced hypertriglyceridemia to the same degree. The VLDL-TG produced by the livers from fructose-treated rats incorporated a much higher percentage of the labelled oleic acid than either control or glucose-fed rats. It is suggested that this finding is due to differences in the enzymatic pathways induced by the different treatments. An unexpected finding demonstrated that the livers from both carbohydrate-fed groups exhibited rates of uptake of free fatty acid (FFA) that were significantly greater than that of the control animals, indicating a possible metabolic influence on FFA uptake. Both carbohydrate groups showed similar increases in this rate. Furthermore, an examination of the relationship between FFA uptake and VLDL-TG secretion revealed that the two processes were linearly related until VLDL-TG secretion reached a plateau. The distribution of the data of the individual groups before reaching a plateau in VLDL-TG secretion also suggests that the metabolic requirements of the hepatic tissue may determine the rate of FFA uptake. It has been accepted generally that cellular FFA uptake is independent of internal cellular metabolism although evidence has been emerging to suggest otherwise. This data presented here appears to be the first suggestion from a perfused liver system that intracellular metabolic requirements of the hepatocyte may influence FFA uptake. Specifically, the balance between esterification and oxidation and the rate at which the fatty acid is metabolized are implicated as possible determinants of the rate of fatty acid uptake.

THE SOLUBLE FACTOR EF-P ENHANCES THE PEPTIDYLTRANSFERASE ACTIVITY OF THE RIBOSOMAL PROTEIN L16 N-TERMINAL PEPTIDE

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Central to the study of the mechanism of peptide-bond synthesis is establishing whether the ribosomal proteins function passively by ensuring correct steric alignment of substrates, or whether they are actively involved in the catalytic process. We have previously shown that ribosomal protein L16 enhances both the peptide-bond formation and the transesterification activities inherent in peptidyltransferase. Furthermore, the unique histidine residue of L16 has to date remained a prime candidate for providing, at least in part, the catalytic activity of peptidyltransferase. Here we show that the N-terminal peptide of ribosomal protein L16, purified from a protease V8 (*Staphylococcus aureus*) digest of L16, exhibits partial peptidyltransferase activity *in vitro*. In addition, we have developed a rapid and large-scale purification scheme for the novel translation factor EF-P which modulates the intrinsic affinity of 70S ribosomes for different amino-acyl tRNA analogues. In this case, EF-P stimulated both the peptide-bond formation and the transesterification activities of the N-terminal peptide of ribosomal protein L16. Further study of mechanistic issues such as these will ultimately aid in our understanding and development of clinically useful antibiotics and other drugs.

DNA-MEDIATED GENE TRANSFER OF THE HUMAN C1 GENE REQUIRED FOR DNA REPLICATION

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The temperature-sensitive (*ts*) mouse L-cell mutant *ts*C1 arrests throughout S-phase immediately after upshift to the non-permissive temperature (npt) due to a defect in DNA replication. The *ts* C1 mutation is recessive and is carried on the X chromosome. DNA-mediated gene transfer of the human C1 gene was attempted in an effort to identify this gene. A co-transfection protocol was employed to decrease the possibility of selecting spontaneous, temperature-resistant (*t'*) revertants. In one system, *ts* C1 cells were transfected with human DNA and the plasmid pSV2neo, which confers resistance to the drug G418. Another system was developed in order to replace the costly G418 treatment with the less expensive HAT selection. A hypoxanthinephosphoribosyl transferase (HPRT)-deficient, azaguanine-resistant, HAT-sensitive (HAT^s) clone was derived from the parental *ts* C1 cells. These HPRT-deficient cells can be complemented by the plasmid pHPT32 which contains the human HPRT cDNA and permits recipient cells to grow in the presence of HAT. The HeLa and 8-Bnpt cell lines were chosen as sources of human DNA. The latter is a *ts* C1/human hybrid containing one human X chromosome; this was confirmed by Southern blot hybridization with an X-specific probe. A total of 30,000 G418^r or HAT^r colonies were screened at the npt, but none of these proved to be *t'* co-transformants.

CORRELATING NERVE FIBER MORPHOMETRY WITH FUNCTION IN FREE MUSCLE TRANSFERS

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Our purpose was to seek a relationship between nerve fiber size or degree of myelination and functional recovery following free, vascularized muscle transfer. Fifteen dogs underwent free replantation of the left gracilis muscle with transection and repair of the motor nerve. After recovery, isometric function was quantified in the replants (R) and the contralateral controls (C). Mean nerve fiber and myelin areas were measured by computerized planimetry from motor nerve sections from both R and C muscles. Relative to C, the R muscles produced significantly less tension (Pt and Po) and also had significantly smaller nerve fibers with less myelin (Table). As well, there was a significant negative correlation between the percent recovery in Po and the R/C ratios for nerve fiber area ($r = -0.75$, $p < .005$) or myelination ($r = -.70$, $p < .01$). No similar relationship held for CT or 1/2 Rt. These data may indicate that the degree of functional recovery following free, vascularized muscle transfer is related to the size and myelination of the motor nerve fibers distal to the nerve repair.

Mean Values for Replants and Controls (mean (S.D.), N=15)

	Pt (N/g)	Po (N/g)	Fiber Area*	Myelin Area*
R	2.1 (.9)+	0.3 (0.1)+	62 (24)+	39 (17)+
C	3.1 (.5)	0.5 (0.2)	85 (19)	55 (12)

*: μm^2

+: $p \leq 0.05$ vs. control

SYSTEM MODELING OF EXCITABLE TISSUES

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The membrane of such excitable tissues as the neuron and smooth muscle has been shown to exhibit resistive and capacitive properties. A quantitative description of these properties in the normal and the disease states yields a wide spectrum of applications in medical science. These properties also help to delineate the mechanism of drug actions and some physiological phenomena such as aging and the intercellular communication through gap junctions in mammals. The quantification of membrane electrical properties requires the use of a suitable model, due to the intricacies and the small size of the tissues involved. Various models had been used to estimate the values of the membrane resistance and capacitance, using the intracellularly-recorded voltage transients of a current stimulation in animals. Unfortunately, accuracy problems often arise in these models due to their reliance on some subjective analysis procedures. The system model proposed here makes use of an alternate representation of the voltage transient (the frequency spectrum). An optimization technique, a non-linear curve-fitting algorithm, is then used to estimate the electrical parameters. This new model has been proven, both theoretically and experimentally, to be more accurate. More importantly, the model provides an objective and reproducible estimation of gap junction resistances and capacitances, which was not possible in the previous models.

HDL BINDING TO ISOLATED DOG ADIPOCYTES FOLLOWING ISOPROTERENOL STIMULATION

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Obese people at risk for coronary heart disease show increased lipolysis and reduced HDL levels. These clinical findings may be explained if augmented lipolysis and HDL binding to adipocytes are linked. To test this hypothesis, we examined the binding of HDL to isolated dog adipocytes following stimulation with isoproterenol, a β -adrenergic agonist. HDL₃ ($d=1.125-1.210$) was isolated from human plasma and radioactively labelled with ^{125}I . Isolated dog omental adipocytes (by collagenase digestion) were incubated in the absence or presence of isoproterenol ($1.0 \times 10^{-5}\text{M}$) and HDL₃ ($10-75 \mu\text{g/ml}$ of incubation medium) for 2 hours at 37°C . Total HDL binding was considered as the amount of trichloroacetic acid-precipitable, cell-associated ^{125}I . Lipolysis was measured by free glycerol release into the medium. While isoproterenol yielded a 6.8-8.4 fold increase in lipolysis, total HDL binding increased by only 2.7%. These results suggest that HDL binding and lipolysis may not be linked and that by inference fatty acids do not interfere with lipoprotein binding to adipocyte lipoprotein receptors.

CHARACTERIZATION OF HUMAN CARDIAC MYOSIN HEAVY CHAIN GENES

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We have isolated and characterized the structure of the genes coding for the α - and β -forms of the human cardiac myosin heavy chain (MHC). Detailed analysis of four overlapping MHC genomic clones shows that the α - and β -MHC genes constitute a total length of 51 kilobases and are tandemly linked. The β -MHC gene, predominantly expressed in the normal human ventricle and also slow-twitch skeletal muscle, is located 4.5 kilobases upstream of the α -MHC gene, which is predominantly expressed in normal human atrium. We have determined the nucleotide sequence of the β -MHC gene, which is 100% homologous to the cardiac MHC cDNA clone (pHMC3). It is improbable that a splicing mechanism is responsible for the divergence of a few nucleotide sequences in the cardiac β -MHC cDNA clone (pHMC3) and a MHC cDNA clone (pSMHCZ) from skeletal muscle. This finding suggests that the same β -form of the cardiac MHC gene is expressed in both ventricular and slow-twitch skeletal muscle. The promoter regions of both α - and β -MHC genes as well as the first coding regions in the respective genes have also been sequenced. The sequences in the 5' flanking region of the α - and β -MHC genes diverge extensively from one another, suggesting that the expression of the α - and β -MHC genes is independently regulated.

BOVINE INTERFERON ALPHA INHIBITS THE MIGRATION OF LYMPHOCYTES FROM BUT NOT INTO LYMPH NODES

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Recombinant bovine interferon-alpha, 1 (IFN- α) was tested for effects on lymphocyte migration in sheep. Chronic lymph drainage methods were used to monitor the efferent lymph of single lymph nodes of conscious animals. When IFN- α was injected into the drainage area of the lymph node or infused directly via an afferent lymphatic, a marked decrease in cell output was observed. Nanogram quantities of IFN- α produced an effect which lasted several hours. To test whether this effect was specific for lymphocytes we first stimulated a lymph node with *Staph. aureus* so that large numbers of neutrophils and lymphocytes were present in efferent lymph. When IFN- α was then injected, the lymphocytes disappeared from efferent lymph but the neutrophils did not. Normal efferent lymph cells were labelled with radio-isotopes and injected intravenously during the IFN- α -induced effect. The entry of lymphocytes from the blood was significantly enhanced at a time coinciding with the suppressed cell exit in the efferent lymph. Recovery data indicated that the lymphocytes were retained temporarily in the lymph node but were not destroyed. Furthermore, the bovine IFN- α does not appear to be antigenic. It is not yet certain whether IFN- α enhances the interactions of cells within the lymph node thereby potentiating immunological reactions. (ackn. MRC & MS, Canada, Ciba-Geigy Ltd., Basle)

SITE-DIRECTED MUTAGENESIS OF THE SARCOPLASMIC RETICULUM CALCIUM ATPASE

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The Ca²⁺-ATPase of sarcoplasmic reticulum is a membrane-bound enzyme which catalyzes the transport of calcium ions across the membrane when coupled to the hydrolysis of ATP. Site-directed mutagenesis experiments were carried out in an attempt to define the amino acids likely to be involved in the coupling mechanism between ATP hydrolysis and calcium transport. Plasmids bearing wild-type or mutated Ca²⁺-ATPase cDNA were constructed and used to transfect COS-1 cells. Microsomes were prepared from the transfected cells and assayed for the expression of immunoreactive Ca²⁺-ATPase and calcium transport activity. The expressed wild-type ATPase enzyme represented approximately 1-2% of the microsomal protein and transported calcium at rates up to 50-fold above controls. Mutation of lysine-297 to methionine, glutamic acid-309 to glutamine, glutamic acid-771 to glutamine, asparagine-796 to alanine, threonine-799 to alanine, aspartic acid-800 to asparagine and glutamic acid-908 to glutamine all abolished calcium transport activity. However, the level of expression of the mutant enzyme was unaffected. All of these mutations which affect the transport of calcium are within the predicted transmembrane domain of the Ca²⁺-ATPase. These amino acid residues may form part of the channel through which calcium is transported across the membrane.

REGULATION OF CELLS IN THE IGE-COMMITTED B CELL SUBSET

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IgE-producing B cells which have been activated and transformed *in vitro* by Epstein-Barr virus invariably express sIgM and sIgD as well as IgE. This co-expression occurs both prior to limiting dilution culture and throughout formal cloning. Such cells retain all 3 epsilon genes in germline configuration on both alleles, with rearrangement of vDJ to the C μ heavy chain locus on the expressed chromosome. Transformed clones secrete all 3 isotypes and express IgM, IgD and IgE in the cytoplasm of single cells. Levels of mu and epsilon mRNA are disparate, perhaps indicative of differential regulation. After 96-120 hours in culture, freshly seeded, washed cells selectively ceased production of IgE, with continued production of IgM. Removal from culture supernatants of IgE reversed the decline in IgE without affecting IgM kinetics. This isotype-specific regulation may reflect the expression of membrane FcERII (CD23) in sIgE⁺ cells, which declines 2.5 fold between 72 and 96 hours of culture. Interactions (binding) between exogenous IgE and FcERII were observed in FcERII⁺ lines which did or did not secrete IgE, but only sIgE⁺ cells were able to bind complexes of soluble FcERII. Such interactions may result in the autoregulatory, negative signal which accounts for the cessation of IgE production.

RECURRENT INHIBITION DURING SUSTAINED SUBMAXIMAL CONTRACTION IN HUMANS

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Increasing recurrent inhibition may contribute to the reduction in voluntary motor unit firing rates observed during sustained contractions. It was the purpose of this study to determine whether the excitability of soleus recurrent inhibitory pathways was increased across fatigue of a sustained submaximal contraction of the plantar flexors. The excitability of these pathways was examined using a modified version of the H reflex technique developed by Hultborn and Pierrot-Deseilligny (J. Physiol., 297:229, 1979). This method involves comparing the amplitudes of a reference H reflex (H_{ref}) and a test reflex pre-conditioned by recurrent inhibition (H'). The voluntary contraction protocol consisted of continuously repeated cycles. Each cycle incorporated both a maximal voluntary contraction (MVC) and a submaximal portion (60% MVC) of constant torque or constant soleus linear envelope electromyography. This contraction protocol produced significant fatigue, as evidenced by MVC torque reduction. Significant reductions in H' amplitude with respect to that of H_{ref} were observed across fatigue. The average amplitude of surface electromyography (AEMG) recorded from the soleus during submaximal contraction declined, while that from the medial and lateral gastrocnemius muscles increased. Tibialis anterior AEMG also increased significantly. It was concluded that soleus recurrent inhibitory pathways were facilitated across fatigue, contributing to the reduction in soleus AEMG and due largely to increasing activity in gastrocnemius motoneurons. It was also concluded that facilitation of soleus Renshaw cells led to the observed co-contraction of muscles acting about the ankle joint. These findings suggest that facilitation of Renshaw cells functions to protect joint stability in the face of muscle fatigue, at the expense of task performance. At the ankle joint, this function would ensure posture maintenance.

ENDOTHELIAL REPAIR: THE REGULATION OF ENDOTHELIAL CELL SPREADING

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Since injury to the endothelium is an initiating event in the development of atherosclerosis, it is important to understand the process by which endothelial cells repair small denuded areas of the endothelium. To study repair, we have used a model of cell spreading in which the response of endothelial cells to mechanical perturbation has been studied following mechanical perturbation of a small portion of the cell periphery by a micropipet attached to a micromanipulator. The cell responds by initially retracting and decreasing in area. This is then followed by the cell spreading back into its original area. The extent of spreading was a function of the duration of time in which the cell was present on the substratum. Specifically, endothelial cells plated for 20 hours were able to recover their original surface area after being perturbed, whereas endothelial cells plated for 40 hours did not. Fibronectin and actin, two proteins involved in cell-substratum adhesion were investigated using immunofluorescence and fluorescence microscopy. The strength of adherence was tested using an adhesion assay in which dishes containing cells were rocked back and forth on a shaking water bath. Endothelial cells plated for 40 hours showed more fibronectin staining than cells plated for 20 hours. There was no difference observed in the pattern of actin staining. Cells plated for 40 hours are more adherent than cells plated for 20 hours. These results suggest that an important condition for the process of endothelial cell spreading is cell-substratum interaction. Thus optimum spreading depends on a reduced interaction with the substratum.

POTENTIAL CALCIUM STORAGE SITES IN FROG MYOCARDIAL TISSUE

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It is generally believed that internal calcium storage sites do not play a role in excitation-contraction coupling in frog ventricular muscle. (Fabiato A., *Am. J. Physiol.* 245:C1-14, 1983; Morad et al, *J. Mol. Cell Card.* 19:527-533, 1987). Yet EM studies have demonstrated the presence of a sarcoplasmic reticulum (SR) with peripheral junctional SR in frog ventricular cells. Since analogous structures in mammalian cardiac muscle have been shown to contain the cardiac SR protein, calsequestrin, believed to be involved in calcium storage and/or release, we were interested in investigating whether frog SR might contain similar SR proteins as seen in mammalian cardiac muscle. Immunofluorescence labeling of cryosections and plastic sections of frog myocardial tissue with affinity-purified antibodies to dog heart calsequestrin was carried out. The results obtained demonstrated the presence of calsequestrin as discrete foci in frog ventricular cells. Double labeling with calsequestrin antibodies and rhodamine-conjugated wheat germ agglutinin (a marker of the cell sarcolemma) suggested that the majority of calsequestrin-containing foci are confined to the subsarcolemmal region of the cell. To test whether the distribution of calsequestrin indeed corresponds to that of the junctional SR in frog ventricular muscle, immunoelectron microscopical studies are in progress.

HOW SYNAPTIC NOISE MAY AFFECT CROSS- CORRELATIONS

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Cross-correlation between input and output spike trains for a repetitively firing neuron are used by some researchers to experimentally estimate the characteristics of an underlying postsynaptic potential (PSP). In this study computer simulation and analytic mathematics were used to explore the effect of synaptic noise on the cross-correlation profile. Noise interval, noise amplitude, and PSP amplitude were varied. Analytic results derived for an ideal case with regular spike noise were helpful in understanding computer-generated results using more physiological noise shape and distribution.

The results of the computer simulations show that (i) synaptic noise significantly decreases the number of displaced counts in the peak in a predictable manner, which leads to potentially significant underestimation of the amplitude of the underlying PSP; (ii) total peak size, not normalized by background counts, is the best estimator of PSP size; (iii) there is no reason to view the cross-correlogram as the sum of 2 terms, one proportional to the PSP profile, and one proportional to the derivative of the PSP profile. The results of this study correlate with experimental results in the literature.

THE EFFECTS OF TEMPERATURE ON K⁺ CURRENTS IN HUMAN T-LYMPHOCYTES

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Voltage-activated K⁺ channels have been implicated in lymphocyte function, including killing and mitogenesis. Cell function is optimal at 37°C whereas studies of ion channels in lymphocytes have been conducted at room temperature. We have now examined $I_K(V)$ in whole-cell recordings from 5 to 42°C. Increasing temperature progressively increased the rates of channel activation and inactivation as well as maximum K⁺ conductance of the cell. At 20°C both activation and inactivation rates had similar temperature sensitivities, whereas at 37°C inactivation rate was much more temperature sensitive than activation rate. In contrast, at 5°C inactivation rate was much less temperature sensitive than activation rate. At all temperatures channel kinetics were more temperature-sensitive than peak conductance. Arrhenius plots for all three parameters were non-linear but with no evidence of a phase transition. Increasing temperature shifted the steady-state activation curve in the hyperpolarizing direction and the steady-state inactivation curve in the depolarizing direction. This resulted in a greater overlap of the curves with a large increase in activatable K⁺ channels at 37°C vs. room temperature. K⁺ currents were well described by Hodgkin-Huxley n^4j kinetics at all temperatures. The effects of temperature changes were fully reversible with no signs of hysteresis over a six-hour experimental period. Hence, channel function is qualitatively and quantitatively different at physiological temperatures and caution should be exercised in extrapolating results from studies conducted at room temperature.

TIME COURSE OF ADAPTIVE CHANGES TO COLD IN DENERVATED BROWN ADIPOSE TISSUE IN RATS

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We investigated the role of sympathetic innervation in the long-term adaptation of brown adipose tissue (BAT), a tissue specifically adapted for heat production in mammals, to cold-exposure and cold-acclimation, by studying the time course of changes in unilaterally-denervated interscapular BAT of rats. In the first experiment, rats were cold-exposed for 1, 3, 6 or 12 days after denervation surgery. Levels of total protein in BAT (an index of tissue growth), GDP binding (an index of the thermogenic state of the BAT), and specific uncoupling protein (an index of thermogenic capacity) increased normally in the half-pads having intact innervation. Denervation reduced, but did not abolish, the effect of cold-exposure, especially after 12 days. In contrast, the increase in total activity of thyroxine 5'-deiodinase (the enzyme converting thyroxine to triiodothyronine) normally seen after cold-exposure was almost totally abolished by denervation. In a second experiment, surgery was performed in rats which had been cold-acclimated for two weeks; rats were then maintained at 4°C for 1, 3, 7 or 14 days after surgery. All four indices of BAT function declined as a result of denervation, with thyroxine 5'-deiodinase activity decreasing at once and UCP levels decreasing the most slowly. Even 14 days after surgery, all indices of BAT function, except activity of thyroxine 5'-deiodinase, were still significantly increased over those levels found in warm-acclimated controls.

We conclude that, except for thyroxine 5'-deiodinase, BAT adaptive response to cold is not entirely dependant upon sympathetic innervation.

THE COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN IS IDENTICAL TO NEUTRAL ENDOPEPTIDASE

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The common acute lymphoblastic leukemia antigen (CALLA) is a 100kd surface glycoprotein which has been identified as a highly diagnostic marker of non-T ALL cells. This molecule is predominantly expressed on leukemic cells, human kidney cells, and on a small percentage of bone marrow cells, fibroblasts, granulocytes and thymocytes. The antigen was purified from normal kidney by immunoaffinity chromatography and elution following SDS-PAGE. The purified protein was digested with CNBr and the peptides generated were sequenced. A lambda-gt10 cDNA library from human kidney was screened with the oligonucleotide probe synthesized from the most suitable peptide sequences. From 8×10^5 clones screened, six were positive; two clones, including #45, were also reactive with a second peptide. EcoR1 digestion of clone 45 generated two major fragments of 0.7 and 1.6kb, and each hybridized with one of the oligonucleotide probes. Nucleotide sequencing confirmed that they contain the corresponding CALLA peptides. Comparison of the CALLA cDNA with all entries in the GenBank database revealed that CALLA is identical to human neutral endopeptidase (NEP) and 95% homologous to the rat or rabbit NEP. Northern blot analysis of RNA from ALL cell lines and human kidney probed with the CALLA cDNA revealed two messages of 6.6 and 3.8kb, while no cross-reactivity was found with mouse RNA. Southern blot analysis suggests that CALLA is encoded by a single gene.

COUPLED MULTIPLE CONVECTIVE STREAMS: A MODEL OF RENAL TUBULAR REABSORPTION OF MOLECULAR WEIGHT INDICATORS

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Secretion and reabsorption in the nephron involves the exchange of molecules across the epithelia of the renal tubule. Of particular interest is the proximal tubular exchange of molecules between the blood, cellular and tubular spaces of the kidney. The multiple indicator dilution (MID) experiment provides a means by which radiolabelled tracers are used to quantify the kinetics of molecular exchange between these spaces.

A mathematical model of this MID tracer exchange was developed to characterize the exchange of tracers as a function of unidirectional steady-state flux coefficients. This model extends previous models of renal MID by treating explicitly the convective motion of both the blood and urine. The kinetic description provided by three partial differential equations was transformed to Laplace space, resulting in a system of ordinary differential equations which were solved in the transformed co-ordinates. Analytical inversions of the Laplace space solutions were performed for various limiting cases of the model, while a general solution was obtained using numerical inversion techniques. Renal MID outflow data (blood and urine) were transformed to Laplace co-ordinates and compared to the Laplace transform of the model solutions to provide a least-squares estimate of the tubular transport function. Such parameter estimation forms the basis for the assessment of tubular disorders from a functional, as opposed to a morphological, approach.

INDIRECT EVIDENCE THAT CRANIAL NEURAL CREST CELLS CONTRIBUTE TO THE DEVELOPMENT OF THE MAMMALIAN THYMUS

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Studies in chick embryos have demonstrated that cranial neural crest (CNC) cells contribute to the development of the heart, craniofacial skeleton and thymus gland in avians. The role of this cell population in mammalian embryos has not been established. However, the observation that retinoids selectively damage CNC cells during the critical period for inducing heart and craniofacial defects in mice has led to the hypothesis that these cells make the same contribution in mammalian development that they do in avians. This hypothesis predicts that retinoid administration during the period of CNC susceptibility in rodents will induce defects in thymus development. In order to test this hypothesis, single doses of retinoic acid were administered to gravid CD-1 mice during stages of CNC cell migration (days 7-11). The fetuses were recovered from these dams on day 18 of gestation and examined for gross external abnormalities and heart defects. The fetal thymus glands were removed, weighed and routinely processed for histological examination. The results demonstrated a reduction in size, and histological abnormalities, in the thymuses of teratogen-exposed fetuses in comparison with controls. The incidence of thymus defects correlated well with the presence of craniofacial and heart malformations. These results are consistent with the hypothesis that cranial neural crest cells play a role in the development of the mammalian thymus.

EXPRESSION OF RETROVIRUS VECTORS IN EARLY MOUSE EMBRYO CELLS

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We are investigating the regulation of gene expression in stem cells of the early embryo. The model system used is the regulation of retrovirus gene transfer vector expression in (i) embryonal carcinoma (EC) cells, which are the stem cells of teratocarcinomas, (ii) embryonal stem (ES) cells, which are normal stem cells of the preimplantation embryo, and (iii) transgenic mice. Retrovirus vectors were designed to express the dominant selectable *neo* gene from different transcriptional promoters. The efficiency of each promoter was tested by infecting EC, ES and fibroblast cells with each vector construct and (i) establishing the relative titre of each virus after *neo* selection; (ii) directly measuring RNA by Northern blot analysis on unselected infected cells. Evidence from our and other laboratories suggests that retrovirus vector sequences inhibit the expression of vector transduced genes in undifferentiated early embryo cells, but not in differentiated fibroblasts. Our experiments show that removal of the retrovirus enhancer sequence does not relieve this restriction. We also show that the human beta-actin gene promoter is transcribed equally well in EC and ES cells as in fibroblasts. However, the *neo* gene is not transcribed in transgenic mice made by infection of preimplantation embryos with the human beta-actin virus. Taken together, these results suggest that, notwithstanding the presence of negatively-regulated vector sequences, it is possible to express genes transduced by retrovirus vectors in early embryonic cells.

PROTECTION OF NEONATAL HEARTS BY REMOVAL OF GLYCOLYTIC END-PRODUCTS AND NUTRIENT SUPPLEMENTATION

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As documented in previous studies conducted in this lab, neonatal myocardium has been found to be more sensitive to global ischemia compared to adult myocardium, as measured by a more rapid-onset time to ischemic contracture (TIC₀). This observation may be explained by metabolic differences between neonatal and adult myocardium. It is suspected that an increased rate of cardiac metabolism in neonates results in a more rapid end-product accumulation than in adults under global ischemic conditions, causing feedback inhibition of anaerobic glycolysis, thus preventing any further glycogen utilization or ATP production. It is expected that the removal of glycolytic end-products and provision of a nutrient source to ischemic neonatal hearts would serve as a means of protection. To test this hypothesis the hearts from 3-day old male piglets were arrested with KCl, excised, and then assigned to 1 of 3 groups. Group 1 was placed in a normothermic (38°C) bath of substrate-free Krebs-Henseleit (SFKH) solution; group 2 was perfused with normothermic SFKH solution; group 3 was perfused with normothermic substrate-enhanced Krebs-Henseleit (SEKH) solution. Hearts in Groups 2 and 3 were also placed in a normothermic bath comprised of the same Krebs solution as the perfusate. A compliant latex balloon connected to a pressure transducer was inserted into the left ventricle of each heart and onset (2 mmHg rise in pressure) and peak TIC were determined.

Group	TIC ₀ (min)	TIC _p (min)
1 (non-perfused)	33.8	55.3
2 (perfused with SFKH)	55.9	86.4
3 (perfused with SEKH)	>180.0	>180.0

Removal of inhibitory metabolites from the heart by perfusion with SFKH served to delay TIC. Additional preservation of the heart was obtained by supplementation with a nutrient source. It can be concluded that the rapid accumulation of glycolytic end-products was one cause for the observed enhanced sensitivity of neonatal hearts under ischemic conditions. This ability to improve the heart's tolerance to ischemia has the potential for future applications to myocardial protection in pediatric surgery.

THE ROLE OF LEUKOCYTES IN ISCHEMIA/ REPERFUSED SKELETAL MUSCLE

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Extensive skeletal muscle necrosis may occur after prolonged ischemia to the lower extremity, with serious consequences both locally and systemically. The extent of necrosis is a combination of cellular damage that occurs during both the period of ischemia and the period of reperfusion. The purpose of this study was to elucidate the role of leukocytes (WBC) in the pathogenesis of the cellular injury associated with ischemia/reperfusion injury. Canine gracilis muscles were made ischemic for 5 hours and then reperfused by normal blood *in situ*. The flux of the WBC into the muscle was determined by measuring serial arterial and venous WBC counts and blood flow, corrected for preischemic muscle weight [WBC flux = (arterial-venous) WBC x blood flow / muscle weight]. Serial muscle biopsies were taken during the reperfusion phase and analyzed for myeloperoxidase (MPO) content as a measure of neutrophil activity. The extent of necrosis in the muscle was determined after 48 hours of reperfusion *in situ* by nitroblue tetrazolium staining. WBC uptake was correlated with necrosis. WBC flux was greatest early in the reperfusion phase and tapered rapidly. With less necrosis, WBC flux occurred later and reactive hyperemia was greater. Myeloperoxidase content was also correlated with necrosis. These findings support the hypothesis that the WBC is instrumental in mediating the tissue damage which occurs during the reperfusion phase following acute arterial occlusion.

PLATELET ACTIVATING FACTOR INCREASES TRACHEAL CARTILAGE COMPLIANCE

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Earlier studies have reported that Platelet Activating Factor (PAF) is capable of inducing airway hyperresponsiveness in guinea pigs and man. We tested the hypothesis that PAF elicits this response through alteration of the proteoglycan structure of airway cartilage. A change leading to an increased compliance of the cartilage would lessen the load on the airway smooth muscle and hence allow the greater constriction of the airway upon stimulation by a contractile agonist. Guinea pigs were repeatedly exposed to an aerosolized solution of PAF for several weeks. Physiologic studies were performed on the excised tracheas in an organ bath system. Tracheas from PAF-exposed animals exhibited passive pressure-volume relationships with steeper slopes than the control animals, the difference being even more evident after the addition of the muscle relaxant theophylline. Isobaric stimulation of PAF-exposed tracheas resulted in greater volume changes over the controls, as was expected, although the difference was not statistically significant with the number of animals studied. Not surprisingly, no difference was observed for isovolumetric stimulation between the two groups of animals, as any change in the cartilage compliance should not alter the force generation of the smooth muscle. These results are consistent with the hypothesis that PAF causes physiological changes in tracheal cartilage compliance, and may account for the observed PAF-induced airway hyperresponsiveness.

PEPTIDOLEUKOTRIENES IN THE CENTRAL NERVOUS SYSTEM

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A study was conducted in conscious cats to measure leukotrienes (LTs) in cerebrospinal fluid (CSF) under physiological conditions and after treatment with compounds expected to affect the synthesis or the disposal of these compounds in the central nervous system.

Samples of CSF (150-320 μ L) were collected via an indwelling intracerebroventricular cannula, from the anterior recess of the third ventricle. They were incubated with a crude preparation of γ -glutamyl transpeptidase to convert any LTC₄ and LTD₄ to LTE₄. LTE₄, expressing the total peptidoleukotriene content of CSF, was measured with a radioimmunoassay technique. Peptidoleukotrienes were found in CSF samples from control experiments in concentrations between 100 and 600 pg/mL, with a mean value of 265 pg/mL. Intravenous administration of probenecid, a compound which inhibits LT removal across the blood-brain barrier, caused a modest rise (31-51%) in LTE₄ levels. Intravenous administration of pyrogen, both bacterial and leukocytic (interleukin-1) had no effect at doses producing an elevation in body temperature. Likewise, pyrogens were ineffective by the intracerebroventricular route.

In summary, this study showed that peptidoleukotrienes are formed in the central nervous system and are measurable in the CSF under physiological conditions. In addition, the results indicate that peptidoleukotrienes are unlikely to play a role in the central mechanism of fever.

A NEW PERSPECTIVE ON UREA CYCLE DISORDERS AND ITS IMPLICATION ON TUMOR PROMOTION

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The present study stems from the observation that orotic acid (OA), a precursor for pyrimidine nucleotides and a normal cellular constituent, is an efficient promoter of both liver and intestinal carcinogenesis in the rat. Nucleotide pool imbalances consisting of an increase in uridine nucleotides and a decrease in adenosine nucleotides have been shown to be critical for OA to exert its promoting effects. Given the fact that each cell has a nucleotide pool geared to its needs, creation of nucleotide pool imbalance could be a common way to achieve promotion in several organs. Levels of OA increase under several conditions of genetic and metabolic disturbances in both animals and humans. One such condition includes disturbances of the urea cycle, due to hyperammonia, deficiency of intermediates (arginine or ornithine) or enzymes (ornithine transcarbamylase (OTC), arginosuccinate synthetase, arginosuccinate lyase, arginase) involved in the urea cycle. The present study was designed to determine whether increased OA seen under some of the above-mentioned conditions (a) causes nucleotide pool imbalance; (b) promotes liver carcinogenesis. The results showed that: (i) arginine deficiency, which decreases the efficiency of urea cycle and results in increased synthesis of OA, created an imbalance in nucleotide pools and promoted liver carcinogenesis in both rats and mice; (ii) high levels of OA seen in sparse fur mutant mice (animal models of human OTC deficiency) were utilized for the synthesis of uridine nucleotides, resulting in a nucleotide pool imbalance in the liver; (iii) liver biopsies from 5 human patients deficient in OTC, who exhibited marked oroticaciduria, showed a nucleotide pool imbalance similar to that seen in the livers of rats under promoting conditions. Interestingly, a few cases have been published wherein liver cancers were found in OTC-deficient patients. These results raise the possibility of whether genetic and metabolic disorders associated with increased levels of OA and consequent nucleotide pool imbalance may pose increased risk of tumor promotion.

IMPROVED MYOCARDIAL SALVAGE WITH TROLOX AND ASCORBIC ACID FOR AN ACUTE INFARCTION

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Trolox (a water-soluble analogue of Vitamin E) and ascorbic acid were found to be more effective free-radical scavengers in myocyte cultures than superoxide dismutase and catalase. Therefore, we tested them in a canine model of regional myocardial ischemia intended to simulate successful thrombolysis and emergency angioplasty (A) in a patient with acute left anterior descending (LAD) occlusion. In 15 to 25 kg dogs the LAD was occluded for 2 hours and then the ischemic myocardium was reperfused for 4 hours (group A, N=10). In this model, 500 mL of deoxygenated saline containing 20 mg EDTA, 2.0 g Trolox (T) and 3.0 g ascorbic acid at pH 7.4 were infused into the ascending aorta 30 seconds before and for the first 3 minutes of reperfusion (group T, N=10). The area at risk (AR) and the area infarcted (AI) were estimated with Evans blue and terazolium staining. In group A, the ratio AI/AR was $25.6 \pm 4.0\%$ which was significantly ($p < 0.01$) greater than the $8.7 \pm 4.0\%$ in group T. These results suggest that the infusion of free-radical scavengers during emergency thrombolysis and angioplasty may salvage jeopardized myocardium and reduce infarct size in patients presenting with an acute myocardial infarction.

NUMERICAL SIMULATION OF STEADY AND PULSATILE BLOOD FLOW THROUGH CONDUITS OF VARIOUS GEOMETRY

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There is considerable evidence that hydrodynamic factors play a significant role in the development and progression of atherosclerosis. The object of this study was to investigate the relation between local flow patterns and the geometry of the conveying vessels. A finite-element program to simulate steady and pulsatile blood flow was developed. Studies on the accuracy and convergence characteristics were done. The flow was described by the continuity and Navier-Stokes equations which represent the conservation of mass and momentum respectively. The mathematical model was verified by comparing numerical results to analytical solutions and physical models. The mathematical model was then applied to blood flow simulations in a number of different situations: (i) pulsating blood flow in a straight cylindrical tube and a tube with axis-symmetric stenosis; (ii) steady flow in cylindrical tubes with various degree of stenosis and flow rate; (iii) an aneurysm; (iv) a two-dimensional model of an asymmetrical Y-shaped bifurcation; (v) carotid bifurcation. The results were presented as velocity-vector plots, streamlines and pressure contours. Comparisons of the theoretical results and the sites of plaques and thrombosis indicate that zones commonly associated with disease coincide with zones of reversed or stagnant flow. In conclusion, although this mathematical model was an over-simplified description of the real flow phenomena, this method yielded good results and can provide useful information about the local flow patterns.

AN OUTFLOW MODEL OF LASER SURGERY FOR TREATING GLAUCOMA

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Glaucoma is a leading cause of blindness characterized by elevated intraocular pressure (IOP) leading to irreparable optic nerve damage. The IOP of a human eye is determined primarily by two factors: (i) the inflow rate of aqueous humor from the ciliary epithelium, which is essentially independent of pressure and remains normal in the glaucomatous eye; (ii) the fluid resistance of the outflow pathway, which is believed to be markedly increased in cases of glaucoma. This study investigated the interaction between the trabecular meshwork, Schlemm's canal and collector channels of the outflow system with a network model which determines the flow distribution and, consequently, the intraocular pressure. The model has the capability to simulate a wide variety of physical alteration to the outflow system, allowing the investigator to predict the effectiveness of various modalities of treatment. When topical drugs are ineffective at controlling IOP in some glaucoma cases, a potential invasive treatment is laser surgery on the trabecular meshwork. The model predicts that the collapse of Schlemm's canal cannot solely account for the large increases in IOP seen in glaucoma, and thus the effectiveness of argon laser trabeculoplasty cannot be fully explained simply as a stiffening of the trabecular beams to prevent canal collapse. Modelling of the effects of YAG laser holes created in the meshwork suggests that only four symmetrically placed holes would be sufficient to completely eliminate the meshwork and Schlemm's canal resistance components. Such a result was not seen in an experimental trabeculotomy study in which four symmetric 1-hour incisions were made on enucleated eyes, which the model predicted would have the same effect as the 4 laser holes. This suggests that local mechanical disruption of the meshwork to create a patency between the anterior chamber and Schlemm's canal also causes widespread weakening of the meshwork which will lead to canal collapse, thus offsetting the benefits of improved access through the meshwork.

MAKING A NEW PLASMID FOR STUDY OF MUTANT PHAGE λ PROTEINS

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DNA terminase is a protein produced by phage λ . It functions by cleaving concatemeric DNA to generate unit chromosomes, and promotes DNA packaging into empty heads. It is made up of two subunits, A and Nul. The Nul subunit was the focus of this study. A number of mutations have been made in the base pair sequence of the Nul gene, thus producing changes in the primary structure of the protein. These mutations will be studied to observe their effect on the various activities of the protein (i.e. binding to DNA, ATP, and the A protein), thus shedding new light on the mechanism of function of proteins in general. In order to study these mutations a new plasmid was needed that would allow sequencing of their base pairs and production of the mutant proteins in sufficient amounts to allow study. This was accomplished by cloning good translation and sequencing start sites into the plasmid at the appropriate locations. The new plasmid was tested and found to have the above-stated qualities.

PART B – CLINICAL RESEARCH

THE COMPARATIVE VALUE OF BONE SCINTIGRAPHY AND COMPUTED TOMOGRAPHY IN DETERMINING BONE INVOLVEMENT BY SOFT- TISSUE TUMOURS

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In seventeen patients with a soft-tissue tumour, the values of bone scintigraphy and computed tomography (CT) in the determination of bone involvement were compared. Bone and CT scans performed for pre-operative staging of the seventeen patients were reviewed retrospectively. The determination of bone involvement by the two imaging modalities was compared to that found at pathology. In all patients studied, the extent of bone involvement was considered equivocal on clinical exam. Thus the determination of the tumour's relationship to the bone by an imaging modality was essential to the selection of appropriate surgical management in each patient. The bone scans were found to have a sensitivity of only 31% with seven false negative and two indeterminate scans. Computed tomography was found to have a much higher sensitivity, 83%, with only two false negative scans. A false negative test is highly undesirable as it may contribute to inappropriate surgical management, incomplete resection and thus local recurrence of soft-tissue tumours. Thus in the determination of bone involvement by soft-tissue tumour, computed tomography was found, in this study, to be a more useful modality than bone scintigraphy.

STROKE RISK AND CRITICAL CAROTID STENOSIS

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Basic data on patients with asymptomatic carotid bruits (ACB) and the incidence of stroke is not complete. Using carotid Doppler, we compared 491 patients with asymptomatic bruits, 646 with TIA without bruits, 255 with TIA and neck bruits, 195 with stroke without neck bruits, 66 with stroke and neck bruits and 500 controls. Doppler-detected carotid stenosis was observed in 39/1000 control arteries. Of the ACB group, 398/1000 arteries had carotid stenosis with a bi-modal distribution at a cut-point of 85% (15KHz). Only patients with severe stenosis had ischemic cerebral events and the severity of carotid stenosis increased prior to the ischemic cerebral events. In the TIA and stroke groups, a similar bi-modal distribution at 85% (15KHz) was observed. The extent and severity of carotid stenosis increased in all symptomatic groups when neck bruits were present. The distribution was not influenced by age and sex. These observations indicate that 85% stenosis of the carotid artery is critical to outcome.

ANALYSIS OF TOPIC COVERAGE IN A YEAR II CLINICAL METHODS PROGRAM

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This pilot study analyzes, in a second-year clinical methods program, the manner of topic coverage which yields the most comprehensive learning experience to students, with the long-term goal of assisting curriculum planners. For the first half of the academic session, topics from six subject areas were chosen for analysis. These were: history-taking and physical examination skills, the cardiovascular, respiratory and abdominal systems, as well as head and neck topics. Four factors were selected as indicators of degree of comprehensiveness of topic coverage: patient-presence, teacher-presence, hands-on experience and reference to literature. During each clinical session, two students from each group filled out questionnaires identifying topic emphasis and extent of coverage. The information was entered into a computer data management system. For the period of time isolated for analysis, results from 243 observations indicated that a large proportion of topics were covered with a clinician and a patient present (72.4% and 80.2% respectively) while the frequency of suggested readings (12.3%) was lacking in general. In addition, the head and neck coverage showed that the scarcity of patients (42.2% of topics) did not interfere with hands-on learning of skills (79.2% of topics). The purpose of these results is twofold. First, they indicate that the degree of comprehensiveness as measured by our four variables depends on the subject area. Second, they provide useful feedback to clinicians and educators.

TRANSPLANTATION OF MICROENCAPSULATED ISLETS OF LANGERHANS AS A METHOD TO REVERSE DIABETES IN THE BB RAT

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Transplantation of microencapsulated islets of Langerhans into galactosamine-induced diabetic rats has been shown to prolong survival and alleviate diabetic complications. These preliminary studies were undertaken to determine if microencapsulated islets would have a similar effect in a model that mimics insulin-dependent diabetes mellitus (IDDM), the BB rat. The BB rat is a good animal model for human IDDM: genetic predisposition, abrupt onset of ketosis-prone diabetes and lymphocytic insulinitis are all features observed with diabetic BB rats. Donor islets were obtained from male Wistar rats by collagenase digestion of the pancreas. After purification, the islets were encapsulated in a semi-permeable alginate-polylysine-alginate membrane to protect them from the host's immune system. Approximately 5000 islets were injected into the peritoneal cavity of each recipient BB rat. Free islets were transplanted into other BB rats as controls. Blood and urine glucose levels and body weight were monitored in both groups of animals after transplantation. The recipients of the microencapsulated islets displayed significantly longer periods of normoglycemia (mean 115 days) as compared to the control group (mean 12 days). This early data suggests that microencapsulated islets may be effective in maintaining normoglycemia in the BB rat and thus has potential as a possible treatment for human insulin-dependent diabetes mellitus.

EXTENT OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), RHEUMATOID ARTHRITIS (RA) AND INFLAMMATORY BOWEL DISEASE (IBD)

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In a previous study, we found that impaired diastolic function (IDF) with normal LV systolic function is common in SLE and is more frequent and severe in active SLE, where it can lead to clinical heart failure. To determine if IDF may be a non-specific response to systemic inflammation, we studied 2 groups of systemic inflammatory disease patients, having either RA or IBD, all of whom had no known cardiac disease and had normal cardiac dimensions, systolic function and clinical cardiovascular examination. The following echocardiographic indices of IDF were measured: isovolumic relaxation time (IVRT) and pulsed Doppler indices of mitral inflow, early (E) and late (A) velocity peaks, ratio (E/A), and mitral pressure halftime (PHT). The results were analyzed in conjunction with the previous data from SLE and normal subjects.

	N	Age	IVRT	E	A	E/A	PHT
Normal	(30)	40	74	0.83	0.59	1.47	65
SLE	(35)	41	89*	0.74*	0.55	1.47	72*
SLE-AD†	(14)		104*	0.69*	0.65	1.18*	74*
SLE-ID†	(21)		80*	0.77	0.48	1.65	71
RA	(10)	53*	80	0.66*	0.61	1.22*	61
IBD	(7)	41	105*	0.69*	0.58	1.22*	59

* p = 0.05 or less compared to Normal

† Active (AD) or inactive (ID) SLE defined by Lupus activity criteria count of >2 vs <2. IVRT, PHT - mSec; E, A-m/s

Prolongation of IVRT (>100mSec), found to be the most sensitive indicator of IDF, was detected in IBD patients. Lowered E and E/A, also indicators of IDF, were found in both groups. However, this finding in RA patients may be due to the age difference. In conclusion, significant IDF is present commonly in IBD patients with no associated cardiovascular disease. A smaller degree of IDF is seen in RA patients. These findings suggest that in these diseases, IDF occurs to a greater extent than previously thought of and may be a non-specific response to systemic inflammation.

PATTERNS OF PULMONARY FUNCTION ABNORMALITIES IN CHILDREN WITH CHRONIC INTERSTITIAL PNEUMONITIS

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Pulmonary function testing is the most sensitive indicator of pulmonary dysfunction in adults with interstitial pneumonitis and/or fibrosis (IPF). This may also be true for children, but the patterns of pulmonary function abnormalities have not been established. Therefore, we reviewed our management of 29 children with IPF. Of these, 17 (59%) were able to perform pulmonary function studies. The age of initial testing following diagnosis was 10.2 ± 1.3 (SE) years. Lung volumes (body plethysmography), maximal expiratory flow rates, diffusing capacity, and arterial blood gases were measured. Group means (% predicted, except PaO_2 in mmHg) and the % of children with abnormal values are tabulated.

	PaO_2	TLC	RV	FEF25%-75%	DLco/VA
Mean $\pm$ SE	68 ± 5	76 ± 4	142 ± 12	78 ± 11	76 ± 3
% abnormal	88%	47%	63%	41%	40%

We conclude that PaO_2 is the most sensitive index of lung function in children with IPFD. 63% of these children also had hyperinflation and 41% had airway obstruction. Nearly half had restrictive disease. Diffusing capacity corrected for lung volumes was abnormal in 40%.

LONG-TERM FOLLOW-UP OF LUMBAR EXTENSION OSTEOTOMY IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Though Smith-Peterson (1945) described a posterior closing wedge osteotomy for the treatment of spinal kyphosis in ankylosing spondylitis, few studies have reported the long-term results of this procedure. We endeavoured to answer two major questions: Considering the chronic and progressive nature of their disease, do patients with ankylosing spondylitis maintain their correction obtained at the time of surgery? In addition, considering the potential risks for morbidity and mortality, are the patients satisfied with the long-term results of this procedure? From 1969 to 1988, the senior author (EHS) performed 105 single level osteotomies in patients with either thoracic and/or lumbar kyphosis. Of these patients, eighty-eight had charts available for review, forty-five were interviewed, and twenty-four consented to a follow-up radiograph of the lumbar spine. Despite the small number of patients contacted, this is the largest series of patients reported at long-term follow-up who had received single level osteotomy for treatment of kyphosis due to ankylosing spondylitis. In review, 83.7 per cent of the patients were satisfied, and 12.3 per cent were dissatisfied. About half felt that they had had no change in posture since their surgery. The remaining half generally felt that their increasing deformity was mild and located primarily in the cervical and/or thoracic spine. Four of the forty-five (8.9 per cent) felt that they had complete loss of sagittal plane correction at an average follow-up of 96.9 months. Analysis of the follow-up radiographs, at an average follow-up of 96.9 months, reveals that eight of twenty-four patients (33.3 per cent) had greater than 10 degrees of sagittal plane correction loss, when compared to the posterior wedge resection attempted at the time of surgery. Loss of correction, either in part or total did not preclude patient satisfaction with the initial procedure.

CORRELATES OF ARTERIAL OXYGENATION DURING EXERCISE IN PATIENTS WITH COPD

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In the present study, we have undertaken a detailed analysis of the respiratory physiological correlates of arterial oxygen saturation (SaO_2) during mild, constant load exercise in 38 patients with severe but stable chronic obstructive pulmonary disease (COPD). Several respiratory physiological variables that would be expected to influence SaO_2 were entered into a stepwise multiple linear regression analysis with mean exercise SaO_2 as the dependent variable. Two variables [diffusing capacity for carbon monoxide (D_2CO) and resting SaO_2] were found to correlate strongly with mean exercise SaO_2 (multiple $R = 0.80$; $p < 0.00001$) and accounted for 65% of the variability among patients. Arterial carbon dioxide tension (PaCO_2) influenced resting SaO_2 but had no independent influence on exercise SaO_2 . Subsequently, the model of mean exercise SaO_2 derived in the present analysis was found to predict accurately mean exercise SaO_2 in a group of 19 similar patients ($R = 0.85$; $p < 0.0001$). While these findings do not establish a cause and effect relationship, they may provide clinicians with further insight as to which patients are likely to desaturate during exercise.

VECTOR COMPUTER SIMULATIONS LINK IMAGING TECHNIQUES TO IN VIVO PHYSIOLOGY

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The potential for vector computer simulations to be used to calculate significant *in vivo* dynamical parameters based on sequential radiological scans is exhibited by this simulation. In the past, computer simulations have been used to model the experimentally-observed renal output of multiple indicators, providing a means to determine the effective whole-organ kinetic constants. In this study a two-dimensional model of renal cortical transport of multiple indicators is simulated on a vector computer by exploiting the natural parallel structure of the filtration process. It is assumed that the kidney cortex can be partitioned into functionally independent units, operating in parallel and having discrete kinetic transport coefficients. Using a colour-coded graphic display, the flow of indicator throughout the kidney cortex for a given set of dynamical parameters is displayed. Thus by using mathematical matching techniques it is possible to determine what spatial distribution of dynamical parameters would create the observed sequence of radiological pictures. These dynamical parameters then provide information regarding not only the anatomical but also the functional status of the organ system in question.

THE APPRAISAL OF LIFE EVENTS: THE EFFECTS OF LOCUS OF RESPONSIBILITY ON EXPRESSED AFFECT

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Recently, research attention has been focussed on the role of cognitive appraisal in influencing the course and outcome of stressful events. For example, Lazarus (1980) points out that challenged individuals are more capable of drawing on personal resources than their threatened counterparts. This paper reports on data collected on a weekly basis from 76 university students (who were also participating in a study of recurrent HSV-1). Each subject was followed for 12 weeks. A weekly life events questionnaire (Marziali *et al.*, 1986) was completed by each subject along with detailed information about importance, desirability, anticipation, prior experience, locus of responsibility, sense of control, helplessness, helpseeking, and affective response. A total of 847 undesirable life events were analyzed; 36% resulted in feelings of sadness. There were three common classes of undesirable events: relationship problems and academic failures, which are mainly loss events, and academic pressures, mainly threat events. Relationship problems and academic failure were the highest risk factor for sadness. Although students were more likely to feel responsible for academic events (failures and pressures) than for relationship problems, locus of responsibility did not influence feelings of sadness. Helpseeking was twice as likely to occur for loss events as for threat events and was not directly related to the nature of the expressed affect.

CONJUNCTIVAL AUTOGRAFT TRANSPLANTATION FOR THE TREATMENT OF PRIMARY AND RECURRENT PTERYGIUM

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A retrospective study of the recurrence rate of pterygia following excision and conjunctival autograft transplantation is presented. Forty eyes of thirty nine patients who underwent surgery over a thirty-six month period were evaluated. Twenty of the pterygia were primary while twenty were recurrent. The extent of invasion onto clear cornea by the pterygium varied from 1.5 centimetres to 7.0 centimetres. With respect to location there were thirty-four nasal, three temporal and three nasal and temporal pterygia. In four cases there was some restriction of extraocular movements. In all cases free conjunctival grafts from the superotemporal bulbar conjunctiva were used to resurface the exposed sclera. There were no intraoperative complications. Post-operative follow up ranged from one month to twenty-five months with a mean of six months. Only three of the pterygia have recurred (7.5%), which compares favourably with the literature (5% to 10%). We recommend this surgical approach as a safe and effective method for treating primary and recurrent pterygia.

VENTRICULAR RESPONSE TO ATRIAL FIBRILLATION: ROLE OF ATRIOVENTRICULAR CONDUCTION PATHWAYS

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The role of the AV node in determining the ventricular response to atrial fibrillation (AFIB) was investigated by comparing atrial (AA) and ventricular (RR) interval variability. Atrial electrograms and surface ECGs were recorded in 18 patients, 12 conducting over the AV node (NODE) and 6 over an accessory pathway (AP) during sustained AFIB. Data were digitized and the AA and RR distributions were measured. The scaling factor ($SF = \text{mean RR} / \text{mean AA}$), or ratio of atrial to ventricular rate, ranged from 2.6 to 5.9 (mean 3.8) for NODE and from 1.5 to 2.5 (2.0) for AP. It was hypothesized that, if the role of the AV node is limited to scaling atrial impulses, RR variability would be predicted by AA variability, and that AV nodes and APs would have similar effects on variability (although with different scaling). The standard deviation (SD) of RR for NODE was predicted by (and on the line of identity with) the product of SF and the SD of AA ($r = 0.78$). The data from AP are on the same line with good ($r = 0.77$) correlation of the combined data. Thus, the coefficient of variation ($CV = SD / \text{mean}$), a dimensionless measure of variability, was not significantly different between AA and RR. For all patients, the maximum (95th percentile) RR interval was strongly correlated ($r = 0.98$) with the product of SF and the maximum AA interval, again along the line of identity.

Conclusions: (1) as expected, AV nodal scaling was greater than AP scaling; (2) RR variability can be accounted for by scaling of AA variability, without invoking further AV nodal contribution to RR variability; (3) this absence of nodal contribution to RR variability is further confirmed by identical AA to RR relationships (with different scaling) for AP patients.

INTRAVENOUS PROCAINAMIDE USE IN THE ELECTROPHYSIOLOGY LABORATORY: LACK OF LONGTERM THERAPEUTIC IMPLICATIONS

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Suppression of ventricular tachycardia (VT) by intravenous (IV) procainamide (Proc) during invasive electrophysiologic testing has been shown to correlate with suppression of VT by oral procainamide. This has led to the widespread use of this agent in electrophysiology laboratories. We wished to determine the longterm implications of the use of the IV Proc. Between October 1979 and January 1985, 27 patients (mean age 54.3 ± 10 years) received IV Proc (mean dose 945 ± 360 mg) in the assessment of ventricular arrhythmias (VT 20, VF 7). IV Proc suppressed VT in 9/27. Previous oral Proc was not predictive of VT suppression. Other effects included VT slowing (55%) (CL 261 to 349 msec), VT termination (15%), new bundle branch block (7.4%) and hypotension (7.4%). 21/27 patients were treated pharmacologically and 6/9 responders to IV Proc received oral Proc (mean dose 3.1 g/day). During a mean followup of 3.4 ± 1.8 years none of these patients remained on Proc, 3 had arrhythmia recurrence and 3 had side-effects. 1/3 nonresponder patients treated with Proc remains on this drug. Arrhythmia recurrence was not predicted by IV Proc response in the electrophysiology laboratory. Patients with VT suppression by IV Proc needed more drug trials (2.89 ± 1.4) than nonresponders (1.93 ± 1.5). Mortality was 18% and 1 of these had shown IV Proc suppression.

In summary, at last followup only 1 patient remains on Proc treatment. Thus, IV Proc use in the electrophysiologic laboratory has very limited longterm therapeutic implications and increases the number of drug trials.

A CASE REPORT OF CHOLANGIOCARCINOMA INVOLVING THE CONFLUENCE OF THE MAJOR HEPATIC DUCTS

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The patient is a 44-year-old caucasian man who had been well all his life. He was first seen by his family physician in October 1988, when he presented with a one-week history of vague generalized abdominal pain, clay-coloured stools and somewhat darker urine. A week later he developed jaundice and complained of pruritus, and was admitted to the local hospital. On physical examination, the patient was obviously jaundiced, his body was covered with scratch marks, and the abdomen was slightly tender upon palpation. Liver function tests were consistent with an obstructive picture, and the abdominal ultrasound suggested intrahepatic duct dilatation although the gall bladder and common bile duct were not visualized.

He was then admitted to the Wellesley Hospital on November 4, and an ERCP showed a normal papilla and the common bile duct. At the common hepatic duct bifurcation a tumour was revealed involving both the right and left hepatic ducts. A CAT scan of abdomen was done on Nov. 10 and showed dilatation of the intrahepatic biliary tree and a hypodense mass surrounding the inferior vena cava (IVC) extending to the porta hepatis. Both the right and left hepatic ducts were drained percutaneously, and the hypodense mass around the IVC was biopsied.

This patient has a provisional diagnosis of cholangiocarcinoma at the bifurcation of common hepatic duct and the alternatives for treatment options at the present moment include: (1) resection of tumour, which depends on the extension of the tumour; (2) liver transplantation; or (3) palliative measures, which include biliary-enteric bypass, or operative intubation in case of incurability, which is determined by the broad infiltration distally and proximally, diffuse or infiltrative type, lymph node enlargement, and intra- or extrahepatic metastases.

Discussion: Tumour of the bile duct occurs infrequently. Approximately 4500 cases develop each year in the United States. Nearly 80% of them are adenocarcinoma, which is also called cholangiocarcinoma, and is not associated with gall stones. An increased risk has been suggested in patients with ulcerative colitis, and in those conditions such as choledochal cyst and papillomatosis. Parasitic infection of the biliary system has been linked to the high rate of cholangiocarcinoma in Oriental populations. The tumour is equally frequent in males and females and it is more likely with increasing age, especially over 60. Jaundice, with or without pain, is present in most patients, and weight loss also is common. Pruritus may be severe, and some patients also complain of fever.

In approximately 60% of patients the tumour was in the upper third of the bile duct, the most difficult area to resect since it is close to the portal vein, hepatic artery and liver parenchyma. 20% of patients had middle third tumour, and 15% had lower third tumours. The remaining 5% had multicentric lesion in the bile duct involving intrahepatic ducts as well as the extrahepatic biliary systems. In view of recent studies, the strategy in the treatment of adenocarcinoma of the proximal bile duct is to resect the tumour radically and to offer patients with unresectable tumours the chance of hepatic transplantation, if extrahepatic tumour growth is excluded. When the tumour is unresectable because of metastasis, a biliary-enteric bypass or an operative intubation can be conducted. Overall, postoperative survival rates were best for the lower-third group (28% at 5 years) and worst for the upper-third lesions (1% at 5 years).

The authors would like to extend their thanks to Dr. N.J. Marcon, Dr. P. Kortan, Dr. G. Kandel, Dr. G. Haber and Dr. R.R. Gray of The Wellesley Hospital for their kind support. We are also grateful to Miss D.D. Leu who typed the manuscript.

A CASE OF CARCINOID SYNDROME WITHOUT ASSOCIATED DIARRHEA

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Mr. D.C., a 58-year-old male, presented to the Emergency Department with an acute episode of shortness of breath (SOB), weakness, flushing of the skin, nausea, anxiety, palpitations and diaphoresis. The episode occurred during physical exertion while he was playing with his grandson. He had had similar – but much less severe – episodes over the previous two years. These minor attacks were triggered by alcohol, emotional upset or physical exertion. Significant negatives included no diarrhea or pallor, no headache or chest pain, no unusual foods and no bee sting.

Past medical history was negative; he had been a very healthy man prior to this time. He had no allergies and was not taking any medications. He did not presently smoke or drink alcohol.

On examination he appeared alert and oriented; he was in respiratory distress. His skin was purple from head to foot; there was no edema. Blood pressure was 70/diastolic; pulse was 80 and regular; respiratory rate was 20 and he was afebrile. Head and neck examination was unremarkable. His chest was clear with good air entry and no wheeze. Cardiovascular exam was normal apart from a III/VI systolic murmur best heard at the LSB and a II/VI diastolic murmur also best heard at the LSB. Abdominal exam showed hepatomegaly with a liver span of 15cm in the midclavicular line. There were no other abdominal findings.

Laboratory investigations showed that he was in metabolic acidosis. EKG and CXR were normal.

Differential diagnosis at this stage was between pulmonary embolism, shock (septic, anaphylactic, cardiogenic) toxic drug reaction, pheochromocytoma or carcinoid syndrome.

Further Investigations: Blood cultures were negative. An echocardiogram showed evidence of tricuspid regurgitation. An abdominal CT scan with contrast showed multiple radiolucent areas in both lobes of the liver (consistent with metastatic disease) and also a mass in the distal ileum that most probably represents the primary tumor. A 24-hour urine showed an elevated HIAA level. A provisional diagnosis of carcinoid tumor with carcinoid syndrome was made. A CT scan-guided liver biopsy was performed.

Discussion: Carcinoid tumors arise from the enterochromaffin cells, predominantly in the gastrointestinal tract, but also rarely in the lung or ovary. These tumors have the potential to produce a variety of biologically-active chemical mediators including serotonin, bradykinin, and histamine, as well as prostaglandins and several neurohormones. Although carcinoid tumors are relatively common the clinical carcinoid syndrome consisting of flushing, shortness of breath, cyanosis, diarrhea and cramping, and pellagra-like skin lesions is rare. The causal relationship between the various compounds released by the tumor cells and the clinical symptoms and signs of the syndrome is far from clearly understood. Flushing of the skin is found in 94% of people with the carcinoid syndrome. A single mediator that causes the carcinoid flush has not been identified. It is not serotonin, since inhibition of serotonin synthesis does not prevent flushing. Diarrhea is found in 80% of patients with carcinoid syndrome. Serotonin – in this case – has been said to be the most likely mediator of the diarrhea since inhibition of serotonin synthesis usually decreases diarrhea. Here we present a case of carcinoid syndrome with a high level of serotonin release (as inferred by the high urinary HIAA level), in which there is no associated diarrhea. Therefore, although the release of serotonin by the tumor may be a necessary condition for the development of the diarrhea associated with carcinoid tumors it does not by itself appear to be a sufficient mediator, and some other as-of-yet unidentified compound may be a necessary accomplice. This other compound is most probably another of the biologically active chemical mediators released from the tumor cells, but could conceivably be a receptor molecule or postreceptor compound through which serotonin exerts its diarrhea-producing effect.

The authors would like to extend their thanks to Drs. G.B. Haber, G. Kandel, P. Kortan, N.J. Marcon, R. Gray and R. Volpé of the Wellesley Hospital and Mrs. Kathy Paré for their help with this project.

PROPHYLACTIC NALBUPHINE IN CAESARIAN SECTION PATIENTS TREATED WITH EPIDURAL MORPHINE

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This study was undertaken to determine if nalbuphine (Nubaine) would prevent pruritis and respiratory depression in post-Caesarian section patients who received epidural morphine. Informed consent was obtained from 60 class ASA I women who were scheduled for elective Caesarian sections. Thirty received a total of 40 mg Nubaine in divided doses by i.v. injection, and 30 received normal saline. All were followed for 18 hours after their Caesarian section with a pulse oximeter to measure oxygen saturation. The blood pressure, respiratory rate, sedation, pain and pruritis levels were recorded at hourly intervals. No difference was found between the study and control groups when comparing blood pressure, pulse rate, respiratory rate, oxygen saturation or pruritis, nor was there a difference in sedation level or pain relief. The results of this study do not support the use of Nubaine as prophylaxis against respiratory depression or pruritis in post-Caesarian section patients who have received epidural morphine.

THE EFFECTS OF DIFFERENT PATTERNS OF CARBOHYDRATE DISTRIBUTION IN NON-INSULIN DEPENDENT DIABETES

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Non-Insulin Dependent Diabetes (NIDDM) is characterized by hyperglycemia, decreased insulin sensitivity, and a tendency to hypertriglyceridemia. Previous studies have shown improvements in these parameters using soluble fibers, slowly-absorbed carbohydrate foods, and enzyme inhibitors. Reports in the early sixties also suggested that taking smaller meals more frequently might have beneficial effects in diabetics. We therefore designed a study to examine the metabolic effects, in 7 Type II diabetics, of taking the same number of calories either as three 400 kcal meals (3M), or as hourly 100 kcal snacks (Nibbling). Each volunteer's caloric intake was determined based on their ideal body weight. The early results from this study can best be summarized as follows:

Time (h)	0	1****	1½*	2	3	4	5***	5½**	6*	7	8	9*	9½*
Mean Blood Glucose (mmol/L)													
Nibbling	8	10	11.6	10.3	10.1	9.2	9.0	8.6	8.1	8	7.7	7.7	8
3 Meals	8	13.4	13.2	12.2	10.3	8.9	11.9	11.6	10.3	8.2	7.2	10.1	10.3
**** p<0.001 *** p<0.01 ** p<0.02 * p<0.05													

These data demonstrate the lower glycemic impact and marked decrease in hunger/satiety variation as a function of smaller, more frequent meals, and suggest that even relatively high carbohydrate intakes by diabetics can have beneficial metabolic effects when taken at an even rate, providing they do not represent an increase in total caloric intake.

A STUDY OF RADIATION DOSIMETRY IN OESOPHAGEAL CANCER TREATMENT

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The goal of radiation therapy is to eradicate the tumour while minimizing damage to surrounding normal tissue. To do this, a known dose must be delivered to an accurately delineated target volume while limiting the dose to adjacent structures. For treating cancer of the oesophagus, particular attention must be paid to sensitive tissues such as the spinal cord, the heart and the lungs. In this project the accuracy of the calculated dose distributions was tested with dose measurements. The experiments involved irradiating a human-like phantom under treatment conditions for a variety of radiation energies. Thermoluminescent dose measurements were made in the target volume as well as the critical tissues. These measurements were compared with those predicted by a CT-based treatment planning computer. The results demonstrate that present dose calculation algorithms compare well at low and high energies within the centre of the beam. However, at high energies (>10 MV) electronic disequilibrium greatly influences the dose in structures both near the edge and outside of the beam. These results suggest additional work is necessary to refine present algorithms to correct for disequilibrium effects.

THE ANATOMY OF THE MEDICAL CURRICULUM MODELLED BY A COMPUTERIZED DATABASE

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Curriculum committees and teachers generally have little information about exactly what is being taught in courses other than their own and how much of their own material is overlapping with other courses. Before new courses and changes are created, they should be based on accurate information on the real curriculum. The development of a software model of the curriculum provides an accurate, centralized and complete description of the core medical teaching including the amount and overlap of material covered. Each and every non-clinical teaching session is described by up to 12 keywords or phrases each having up to 40 characters in length, which were collected by students in the school year of 1986-87 attending the actual teaching sessions, resulting in a total of 18,000 keywords. After they were entered into an IBM AT-compatible computer system, custom application software, written in a database language, was used to structure the data for retrieval. By using the keywords of a particular course to search the entire curriculum for similar occurrences in other courses, overlap could be easily characterized. This resulted in Pathology, Physiology and Gross Anatomy being the top three courses with most overlap. Respectively, 8.7%, 8.4% and 7.9% of their curriculum content could be found outside of their teaching in other courses. The course with the least overlap was Medical Ethics, representing only 0.2% of its content in other courses. By using a computerized statistical procedure called factor analysis, the courses could be grossly grouped into six categories by nature of similar overlaps: the *Biochemistries*, the *Anatomies*, the *Pharmacologies*, the *Histologies*, the *Pathologies*, and *Community Medicine*. These results provide medical educators with a gross overview of the status of curriculum, which is vital information before change is to be implemented.

A COMPARATIVE REVIEW OF THE MAGNUSON-STACK AND PUTTI-PLATT OPERATIONS FOR RECURRENT ANTERIOR DISLOCATION OF THE SHOULDER

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A comparative functional analysis of 18 operative cases for repair of recurrent anterior shoulder dislocations, consisting of 9 patients who underwent the Magnuson-Stack procedure and 9 patients who underwent the Putti-Platt procedure at a Toronto community hospital, was performed. Range of motion, strength, stability, pain, relative function and complications were assessed in all patients with an average follow-up of 39 months. Pre- and post-operative x-rays were reviewed for Bankart and Hill-Sachs lesions, and other degenerative changes.

The data indicated that excellent results were obtained in 5 of the patients who underwent the Magnuson-Stack procedure, and in only 2 of the patients who underwent the Putti-Platt procedure. Range of motion and strength were most limited in the Putti-Platt group. While Bankart and Hill-Sachs lesions were not consistent pathological findings in either operative group, subscapularis laxity was a suggested common cause of recurrent shoulder instability in both groups. Overall analysis of results favours the Magnuson-Stack repair over the Putti-Platt in this series.

DETECTION OF PREVIOUS DEEP VEIN THROMBOSIS WITH VENOUS DOPPLER AND PHOTOPLETHYSMOGRAPHY

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Ascertaining whether patients had previous silent or non-objectively proved deep vein thrombosis (DVT) could affect their future management. To evaluate the reliability of two noninvasive tests, the photoplethysmograph (PPG) and venous Doppler, we performed a blinded, retrospective cohort study of patients with objectively confirmed (DVT+) or refuted (DVT-) previous episode(s) of DVT. 28 of 33 DVT+ patients had abnormal PPG and/or reflux by Doppler whereas 39 of 49 DVT- patients had normal PPG and no Doppler reflux (sensitivity: 85% and specificity: 80%). Of 33 DVT+, 21 had abnormal Doppler results (sensitivity: 64%), in contrast to 45 of 49 DVT- with normal findings (specificity: 92%). Moreover, 23 of 33 DVT+ patients showed abnormal PPG results (sensitivity: 70%) whereas 40 of 49 DVT- had normal PPG (specificity: 82%).

Based on our findings, the presence of reflux with Doppler is very specific for previous DVT. Furthermore, the presence of normal PPG and Doppler is reliable for excluding previous DVT. Abnormal PPG with normal Doppler findings, however, is an unreliable predictor of previous DVT. Nevertheless, this occurred in only 13 of 82 patients. Therefore, the combination of PPG and venous Doppler can reliably predict the absence or existence of previous DVT in most patients.

EVALUATION OF THE HEALING OF HUMAN SURGICAL WOUNDS BY MEANS OF ELECTRICAL RESISTANCE OF SKIN

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Previous methods of evaluating the healing of surgical wounds include the measurement of tensile strength and histologic analysis, but they are only practical in animal models. The commonest way of assessing human surgical wounds is visual inspections, which by nature is subjective and qualitative, and thus inappropriate as a method for evaluating the effectiveness of agents that can be used to enhance healing. We have developed a new non-invasive method of monitoring the healing of standard incisions by measurement of the electrical resistance of skin. Electrical resistance was measured via surface electrodes placed over several sites along the incision. Recordings were taken at intervals of time after surgery, beginning on the second post-operative day and continuing for several weeks. In addition to the electrical measurements, the wounds were assessed clinically by an independent observer for the purpose of correlating electrical resistance with the clinical impression of a wound.

Preliminary analysis of data from 19 of 55 patients studied suggests that electrical resistance falls to 1% of normal values in the immediate post-operative period (first 48 hours), and returns to normal sometime between 15 and 30 days. We believe that it is possible to predict which patients are fast or slow healers on the basis of readings taken in the first fifteen days, and that this new method involving the measurement of skin resistance can be used clinically to study wound healing in humans.

EVALUATION OF BEDSIDE TESTING IN HEMISPATIAL NEGLECT

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Neglect is a neurobehavioural disorder in which patients fail to respond to information from the side of space contralateral to brain damage. It is more common and severe with right brain damage (RBD) and can be a major impediment to rehabilitation. This project evaluated different tasks frequently used in the assessment of neglect behaviour at the bedside. We report results on 27 patients (13 RBD and 14 LBD) with acute unilateral hemisphere stroke confirmed on C.T. scanning, and 20 age-matched controls. Bedside tasks included line drawings (e.g., a daisy), bisection of horizontal lines, cancellation of lines, letters, and designs arrayed on a page, and visual search of pictures on a large board. Lesion size was digitized on each C.T. slice and location determined by comparison to a C.T. atlas. A three-way analysis of variance was conducted for each task, and performance was correlated with lesion size and location on C.T. and neurological scores. The RBD group showed deviation to the right on line bisection ($p = 0$) but no significant difference emerged on the line cancellation task. On letter and design cancellation, there was a significant group effect due to the left-sided omissions of the RBD group ($p = 0.01$). On visual search, LBD and RBD patients were equally impaired in searching for items ipsilateral to their stroke. Five RBD patients showed left-sided neglect on line drawings as well as the other tasks. No correlation with lesion size, location, or neurological score was found on any of the tasks. We conclude that, if patients show neglect on drawings, further tests are unnecessary. For those who do not, line bisection or letter and design cancellation are the most useful for detecting hemispatial neglect and for following its clinical course.

PART C – COMMUNITY HEALTH

A REVIEW OF MOTORCYCLE PATIENTS ADMITTED TO A REGIONAL TRAUMA UNIT

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The number of licensed motorcyclists within the Province of Ontario continues to grow annually. In the last 3 years the Sunnybrook Medical Centre Regional Trauma Unit (SMC RTU) alone has treated over 128 patients for serious multiple injuries as a result of motorcycle accidents. This accounts for approximately 10% of SMC's total trauma population. Because there is an absence of literature which focuses on Canadian motorcycle accident statistics, this paper is being offered as a descriptive account of one hospital's experience and may be useful as a base to stimulate interest in continued research into this ongoing problem. Cases over a 28 month period ending December 1987 were reviewed to determine if any trends were evident amongst the trauma population of motorcyclists. It was expected that because there was an increase in motor vehicle-related traumas this would also hold true for motorcycle accidents. In fact, what was observed was a decrease in the actual number of cases admitted to the RTU over the past 3 years. The largest body of the population consisted of young males under the age of 25 (68%). Of the motorcyclists with injuries significantly serious to warrant admission to the Trauma Unit, 16% died, while an additional 50% went on to other facilities for further rehabilitation. Other indices such as time of day and week of incident, helmet use, disposition and disability, length of hospital stay, referral patterns, transport time and Injury Severity Score (ISS) were also observed. As was anticipated, a high percentage of patients sustained lower limb injuries (30%). Not surprising was the fact that 80% of these patients received some form of head injury which appeared to be unrelated to the incidence of helmet use. Outside of the above noted injuries, there does not appear to be one predominant body system or region which is routinely traumatized.

RISK FACTORS ASSOCIATED WITH UNDERNUTRITION OF ETHIOPIAN CHILDREN

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Despite recent advances in nutritional supplementation and oral rehydration therapy of acute diarrhea, malnutrition and its sequelae remain a significant global health problem. The aims of this study were to determine the prevalence of undernutrition among a group of Ethiopian children and to identify associated risk factors. Anthropometric measurements of nutritional status (height, body weight, head circumference, mid arm circumference, and triceps skin fold) of children under five years of age and a questionnaire completed by personal interview of the children's parents were performed in three urban and three rural areas of Jimma, Ethiopia. Point prevalence of undernutrition was higher among children living in rural areas ($n = 98$) compared to the children who were residing in villages ($n = 116$), as determined by mid arm circumference (64.9% versus 35.8%), triceps skin fold (37.4% vs. 4.4%), and weight-for-height (12.1% vs. 7.9%). In addition to rural residence, other factors that were significantly associated with childhood undernutrition included fathers' occupation as a farmer, parents eating meals with their children, smaller family size, and a lack of a clean water supply. Knowledge about, and the use of, oral rehydration solutions for the treatment of acute diarrhea was not different among families with undernourished children. We conclude that children in rural Ethiopia are at greater risk of undernutrition. Social factors appear to also be important determinates of undernutrition in these children.

LEVELS OF DISABILITY IN TWO NATIVE COMMUNITIES IN NORTHWESTERN ONTARIO

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Following the 1980 Royal Commission on Disability in Canada, interest has been focused on the levels of disability in the Canadian population. In June 1986, the Health and Activities Limitations Survey (HALS) was administered by Statistics Canada to most sectors of the population. A modified questionnaire was used for Northern areas, including some Indian Reservations. Not all bands of Native people were covered by this survey. The purpose of our study was to determine the levels of disability in two such communities in Northwestern Ontario, and to use this information to advise the Band Councils of these communities.

We based our survey on the HALS questionnaire (modified for Northern areas) but we modified some of the questions to suit the conditions on the Reserves. We administered the survey on two Reserves in the Sioux Lookout Zone, Deer Lake and Sandy Lake. We report here the results of a preliminary analysis. In Deer Lake, the rates of disabilities were 29.0% for adults (people 15 years of age or older) and 10.8% for children. These rates are more than twice the national average, as reported by Statistics Canada. In Sandy Lake, the disability rates were 20.3% for children, 21.6% for adults aged 15 to 30, 41.1% for those aged 30 to 50, and 82.6% for those aged over 50. The rates of disabilities were much greater than the Canadian average for each age-group studied. Females less than 30 years old had slightly lower rates of disability than males of the same age; for those greater than 30 years old, the disability rates were about equal. The overall rate of disabilities at Sandy Lake was 30.0%, which is more than twice the Canadian national rate of 13.2%. We conclude that the level of disabilities on these two reservations was much greater than that seen generally in Canada. We suggest that this may be due to limited access to medical treatment and rehabilitation services.

AWARD WINNERS

In conjunction with the Undergraduate Medical Student Research Day, a competition is held. This year, the judges were Drs. Whiteside, Murray, Salerno, Wiley, and Bayliss. The participants and organizers of the Research Day would like to acknowledge the effort put in by these hard-working judges, and thank them for their work. (Dr. Salerno deserves particular mention for his address at the banquet held the evening of the Research Day. It was up to his usual inimitable standard.)

The following students were judged to have produced the most outstanding presentations and were presented with the George Brown Memorial Award, including a prize of \$250:

Shelley Boyd 9T2	Vicky Chen 9T0	Dae-Gyun Chung 9T2	Ellen Grant 8T9	Gyl Midroni 9T0
Betsy Quackenbush 9T1	Dominick Shelton 9T1	Andrew Smith 9T0	Raymond Shu 9T0	Bach Vu 9T0

Vicky Chen was also awarded the Gerald Wrenshall Book Prize, with a value of \$50.

The work of Shelley Boyd, Gyl Midroni, and Bach Vu was considered particularly outstanding and they were selected to attend the 30th Annual Student Research Forum held in April 1989 at the University of Texas. Their expenses were generously supported by the Medical Alumni Association.

Research Day (contd)

many important subjects. Practically nothing about how nerves regenerate, about memory and consciousness, about how embryos develop, about the control of cell growth, about how cells age or die, about why some people smoke or drink to excess, about depression or mania.

Then I think of the effort that went into doing the projects. Perhaps finding out for the first time how research is done. Running a literature search and using the Citation Index. Reading the two dozen papers that turned up in the search. Screwing up the making of the first buffer solution and wasting 3 whole days before realizing the mistake. Learning to use the spectrophotometer, the pH meter, the scintillation counter and the Mac computer. Finding out that a key instrument was on the blink and could not be repaired for 2 weeks, and that an essential control had been omitted. Yes, positive and negative controls, there's another important aspect of science. Not much was said about these in lectures. Doing research and passing examinations are certainly two quite different activities.

Then all the interactions with people that were involved. Finding out that the Supervisor is really quite human after all. And that some of these graduate students are really smart and helpful and are also fantastic softball player. As for the Post-Docs, these guys are the fountain of knowledge!

And I think of all the experiments that were involved. Perhaps adding inhibitors to the cells in tissue culture at 4 h intervals throughout the day and night. Or, just before the summer was over, doing a Southern blot and finding that the pattern shown by the tumor cells was quite different from the control. Yes, it was a small finding, but no one had ever observed it before. A graduate student is going to follow it up over the winter. Apparently there's a chance that a paper will come out of it eventually, but a lot more work has to be done. It's astonishing how much work and effort goes into writing a good paper.

Then the prizes for the winners. It's too bad everyone can't get a prize. And some really lucky participants get a chance to compete

down in that research competition for medical students in Galveston. I know that entrants from U. of T. have done remarkably well in previous competitions. Then I wonder how many of the participants will actually carry on research down the road. It's too early to tell that, but I'm sure that all the participants, whether they are committed to research or not, have learned new and valuable ways of looking at problems. And that in itself is what it's all about.

Yes, these are some of the things I associate with Research Day.

R.K. Murray

Cardiovascular Research Symposium (continued)

tion of photoplethysmography and Doppler reflux flowmetry reliably predicted the absence or presence of previous deep venous thrombosis in patients. Such non-invasive assessment could be useful in future management.

Heart disease in obesity correlates with increased lipolysis and decreased high density lipoproteins. Eric Grief found that these may be independent risk factors, controlled by different mechanisms, with independent implications for therapy.

In a study of cold cardioplegia, Robert Gatley found that the quality of myocardial protection provided by histidine buffering was 60-fold better than that provided by Tris buffering. Histidine is a natural blood buffer and could become routine in future formulations of cardioplegia.

Douglas Ing assisted in characterizing human cardiac myosin heavy chain genes. This work in molecular cardiology will illuminate the basic causes of a variety of cardiomyopathies in the future.

Neonatal myocardium may be more sensitive to ischemia than adult myocardium. Dominick Shelton found that a more rapid accumulation of glycolytic end-products can be reversed in neonates by continuous perfusion of a substrate-enhanced washout solution. This has applications in pediatric surgery.

Carl van Walraven found that Trolox and ascorbic acid are free radical scavengers which

may salvage ischemic myocardium. Future application may be in reducing infarct size in patients with acute myocardial ischemia.

In a study of Doppler-detected carotid stenosis by Shabir Bhimji, the combination of greater than 85% stenosis, symptoms and neck bruits produced the greatest risk of stroke. These and continuing observations will determine optimum therapy in the future.

Grace Chua shed doubt on the reliability of small-animal models of volume overload congestive heart failure caused by aorto-caval shunting. Only 20% of rabbits and no rats survived to develop failure. The greater tolerance of dogs to this procedure should favour future models.

Skeletal muscle necrosis is due to both ischemia and reperfusion. Andrew Smith found that leukocytes in reperfused muscle correlated with extent of necrosis. Future studies will determine the mechanisms by which leukocytes mediate tissue damage.

Impaired diastolic function of the heart may be a non-specific response to autoimmune inflammation. Varaporn Chiamvimonvat confirmed this in a clinical study of patients with lupus, rheumatoid arthritis and inflammatory bowel disease. This new index of suspicion may alert clinicians to the presence of these diseases in the future.

Paul Wong showed the value of mathematical modelling in rheology by simulating local flow patterns characterizing atherosclerotic vessels in physical models. His numerical simulations confirmed the location of zones of reversed and stagnant flow which promote atherosclerosis.

Summary

This focus on the cardiovascular sciences was rated a success by the students, the organizers and the audience. The symposium provided an additional opportunity for scientific dialogue beyond that of the poster presentations themselves. The final reward was an excellent dinner at Massey College for all participants.

Dr. Colin E. Bayliss

Chairman

Cardiovascular Research Symposium

